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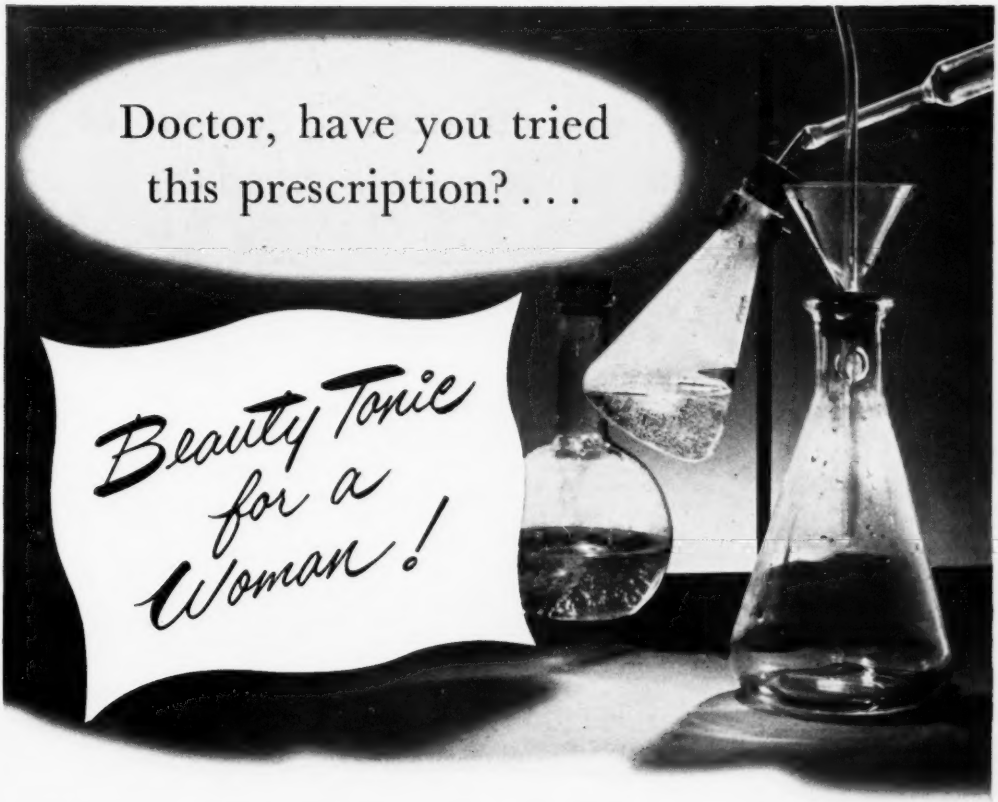

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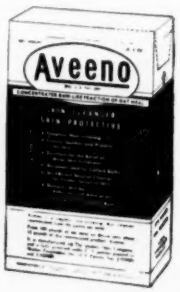

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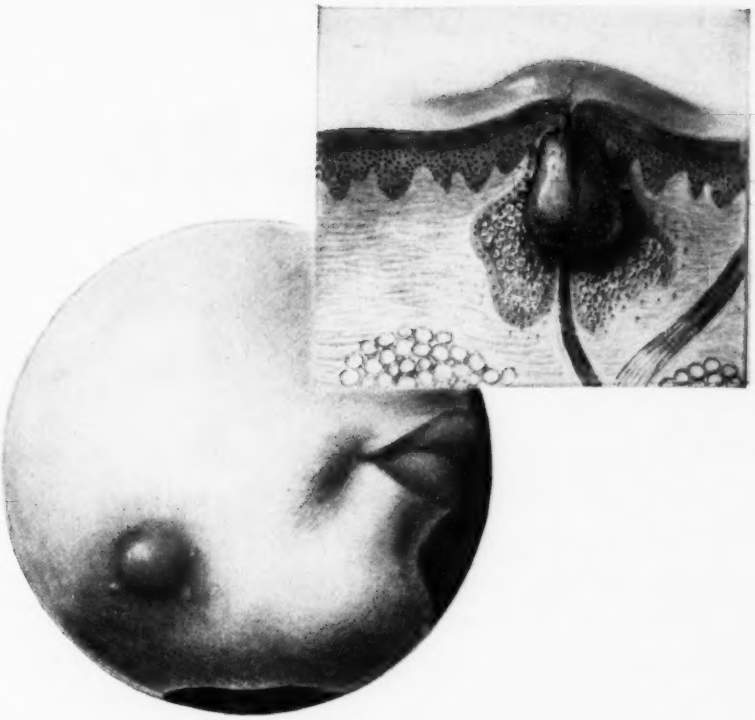

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1 Halpern, Alfred: The Hydrophilic Absorption Ointment Bases, J. Am. Pharm. Assn. XII, pg. 83 (Feb.) 1951.

2 Perrin, Samuel R.: Clinical Safety of Polysorb, Postgraduate Med. 8:485 (Dec.) 1950.

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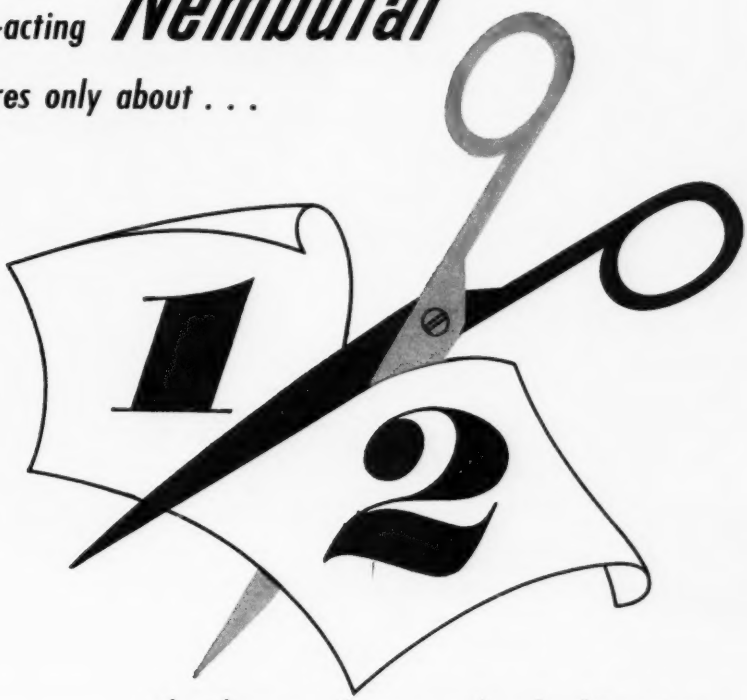

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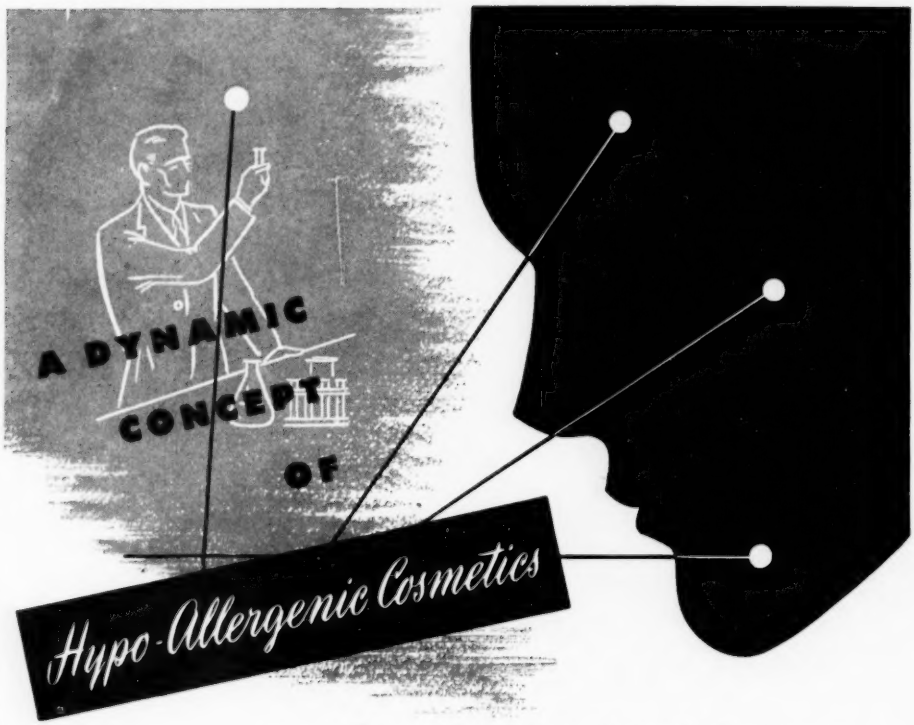

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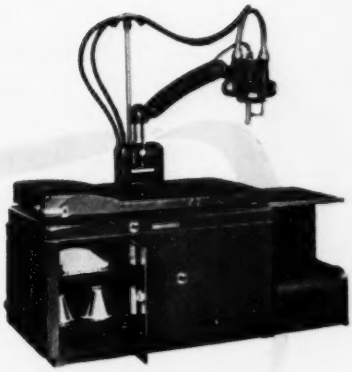

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Archives of Dermatology and Syphilology

VOLUME 65 MARCH 1952 NUMBER 3

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LOCAL DEPILATORY ACTION OF SOME UNSATURATED COMPOUNDS

PETER FLESCH, M.D., Ph.D.
PHILADELPHIA
AND
MADISON HUNT, Ph.D.
WILMINGTON, DEL.

IN A PRELIMINARY report [1] we described the local depilatory effect of the intermediary polymers (dimers) of chloroprene. When painted on the skin of laboratory animals, in all species tested these compounds caused reversible baldness at the site of application. In vitro the dimers inactivated the free sulfhydryl groups of glutathione, human epidermis, and liver homogenates in concentrations which corresponded well with the in vivo depilatory concentrations.[2]

We attributed the —SH-inhibitory action of the dimers to the unsaturated bonds in the molecule which tie down the —SH groups according to the equation [3]

$$-CH=CH- + RSH \longrightarrow RS-CH-CH_2-$$

On the assumption that the depilatory effect was related to the —SH-inhibitory action of these compounds, we tested a number of unsaturated compounds for their depilatory effectiveness. The substances tested fulfilled the following requirements: 1. All compounds had the —CH=CH— grouping. 2. None of the compounds contained Cl and thus did not give rise to the HCl formation which had greatly contributed to the irritating effect of the dimer. 3. All compounds were of known composition, chemically pure and stable.

This paper deals with the effect of some synthetic and some naturally occurring unsaturated compounds upon hair growth in laboratory animals. Several of these compounds were tested in vitro for their —SH inhibitory activity. The findings are reported because they may have a bearing on normal hair growth and keratinization.

This work was done in part under a Damon Runyon Senior Clinical Fellowship of the American Cancer Society, Inc.

From the Department of Dermatology and Syphilology, University of Pennsylvania School of Medicine, and Jackson Laboratory, E. I. DuPont de Nemours & Co.

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METHODS

The unsaturated compounds tested in laboratory animals could be divided into three groups: (1) synthetic compounds with the allyl (—CH=CH—CH_2—) grouping: allyl alcohol, allylurea, allyl ether, allyl propionate, thiosinamine (allylthiourea), hexamethylene tetramine allyl iodide, allyldiphenylacetic acid, allyl diphenylacetate, allyl laurate, allyl benzoate, hexadecene-1; (2) synthetic compounds with the vinyl (—CH=CH—) grouping: isoprene, vinyl 2-ethylhexyl ether, di-2-ethylhexyl maleate, 1-vinylethynyl cyclohexanol, cetyl methacrylate, and (3) naturally occurring unsaturated compounds: vitamin A and squalene.[4]

In screening tests 0.1 ml. of each compound was applied to five mice. The solid compounds were used in saturated alcoholic solutions. A single dose was applied, without rubbing, between the ears and on the upper backs of the animals, as these areas are inaccessible to licking or scratching. No attempt was made to remove the hair mechanically; the term "depilation" in this study means spontaneous loss of hair.

If the mice lost their hair, further tests were carried out in guinea pigs and rabbits by local application of 1 ml. each of these compounds. All animals were observed every other day over a period of three weeks.

Vitamin A was tested only in mice, as hair loss in other species following local application has been described previously.[5] Both the natural esters (E. R. Squibb & Sons) and synthetic vitamin A palmitate (Abbott Laboratories) were tested. The natural esters were applied every other day in 10 doses, each containing 6,600 units in 0.2 ml. of a 1:2 mixture of corn oil with absolute alcohol. A control group was treated locally with the solvent. Synthetic vitamin A palmitate was dissolved in alcohol, and five local applications of 1,000 units each were given every other day. The control group received topical treatment with absolute alcohol.

Histologic studies were carried out in depilated mice and guinea pigs at the height of the hair loss. The sections were stained with hematoxylin and eosin. Biopsy specimens from a rabbit treated with squalene were removed 24 hours after treatment and then every other day for three weeks. Two biopsy specimens, one before treatment and one 24 hours after application of squalene, were also stained with Bennett's reagent for sulfhydryl groups.[6]

4. Allyldiphenyl acetic acid and allyl diphenylacetate were obtained through courtesy of Glenn E. Ullyot, Ph.D., Smith, Kline & French Laboratories. Synthetic vitamin A palmitate was generously supplied by Abbott Laboratories. The other compounds were supplied by E. I. DuPont de Nemours & Co.

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Sulfhydryl groups were determined with Anson's method [7] and with Bennett's reagent.[8] Determinations were carried out after incubating glutathione (40-60 γ), 20% buffered (pH 7.4) homogenates of isolated human epidermis,[9] and 10% homogenates of guinea pig and mouse liver with the in vivo active unsaturated compounds. Serial dilutions of the unsaturated compounds were prepared with absolute alcohol. The reaction mixtures were shaken for 15 minutes at frequent intervals at room temperature before the determinations were carried out. Control solutions contained absolute alcohol in place of the unsaturated compound.

Succinic dehydrogenase activity was measured in guinea pig and mouse liver homogenates with the method of Kun and Abood.[10] We incubated 1 ml. of 10% tissue homogenate for 15 minutes at room temperature with 0.1 ml. of alcoholic solutions of the unsaturated compounds. Control solutions contained 0.1 ml. of alcohol.

RESULTS

Of the substances tested, the following caused hair loss: allyl benzoate ($C_6H_5CO—O—CH_2—CH=CH_2$) in all mice, allyl laurate ($C_{11}H_{23}CO—O—CH_2—CH=CH_2$) in all mice and guinea pigs, allyl diphenylacetate [$(C_6H_5)_2CH—CO—O—CH_2—CH=CH_2$] in three out of five mice and in one out of four rabbits, vitamin A in all mice, and squalene in all guinea pigs and rabbits.

Hair loss from the different allyl derivatives followed essentially the same course in all animals. Two days after application of the allyl compound the skin became thickened; toward the end of the first week crusts appeared at the site of application, and the hair was cast off in the form of tufts with the roots attached. In contrast to the depilation caused by the dimer,[2] the underlying skin was frequently denuded of its epidermis, crusted, and hemorrhagic. The hair loss was limited to the site of application (Fig. 1). In all instances the hair loss was reversible. Two weeks after application of the depilatory agents the hair began to regrow, and within four weeks the normal appearance of the fur was restored.

The allyl compounds were highly toxic to mice after local application. Detailed toxicologic studies were beyond the scope of this study; in our preliminary experiments 0.1 ml. of these compounds killed all mice within 24 hours, even in a 50% concentration. As a routine depilatory dose, we adopted the application of 0.1 ml. of the 10% concentration. This dose was well tolerated by all animals. Fifty per cent of the rabbits were killed by 1 ml. of allyl laurate and of allyl benzoate applied to the skin; the same dose of allyl diphenylacetate was well tolerated. Guinea pigs appeared to be more resistant to the allyl compounds, and all survived the local application of 1 ml. without any apparent ill effect. Hair loss in guinea pigs following allyl laurate was incomplete (Fig. 2).

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7. Anson, M. L.: The Sulfhydryl Groups of Egg Albumin, J. Gen. Physiol. **24**:399 (March) 1941.

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Vitamin A was well tolerated in the doses applied. Both the natural and the synthetic compounds caused hair loss (Fig. 3). The depilatory action of the vitamin differed from that of the other compounds in several respects: 1. The first signs of baldness appeared toward the end of the second week. 2. While it was possible to keep animals continuously bald by repeated applications of allyl compounds or of chloroprene dimers, the hair of the vitamin-A-treated animals regrew in spite of

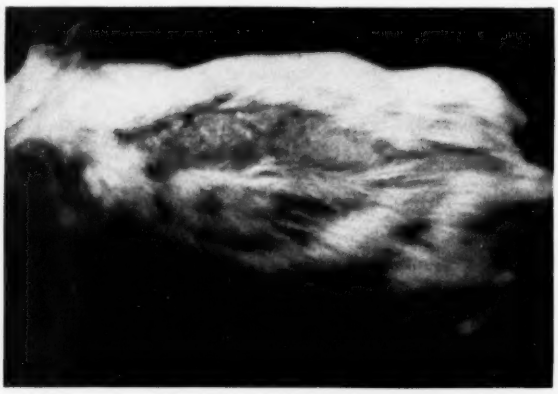

Fig. 1.—Hair loss in mouse after single local application of allyl benzoate.

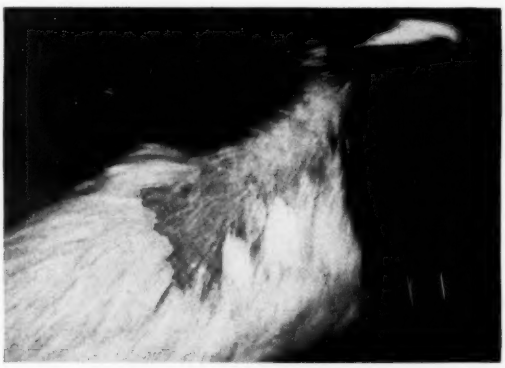

Fig. 2.—Partial hair loss in guinea pig after single local application of allyl laurate.

continued treatment. This is in agreement with previous observations.[11] 3. There were only minor signs of inflammation after topical application.

Hair loss from squalene has been described in a previous publication.[12] The hair loss is reversible, limited to the site of application of the compound, and not accompanied by gross or microscopic signs of inflammation. In control groups of

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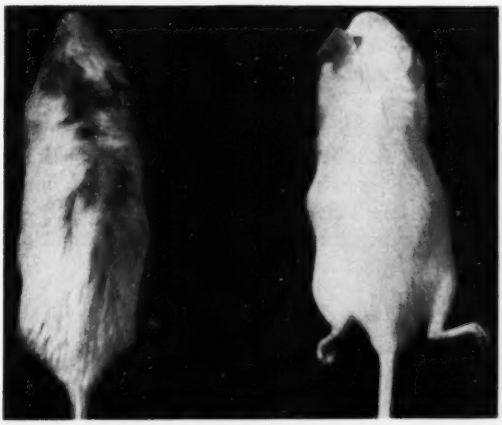

Fig. 3.—Left, hair loss in mouse after local application of synthetic vitamin A palmitate. Right, control.

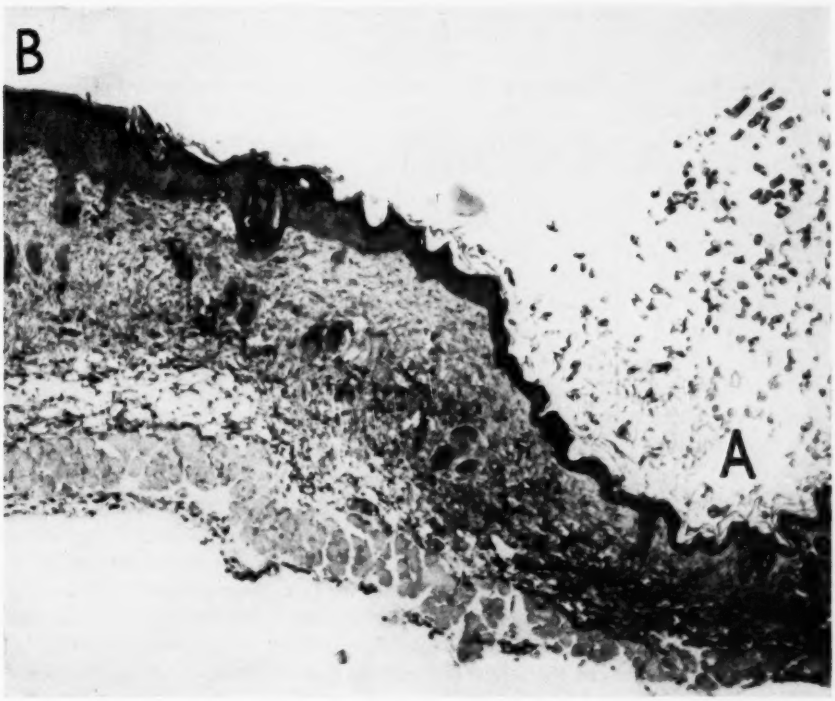

Fig. 4.—Mouse skin 14 days after treatment with allyl laurate; *A*, normal skin; *B*, treated area with hyperkeratosis, thickening of the epidermis, disappearance of the superficial hair follicles, and hyperplasia of the deep follicles; × 80.

rabbits, treated with liquid petrolatum, no alopecia developed, indicating that the depilatory effect of squalene cannot be attributed to its physical action.

The histologic findings after application of the allyl compounds in mice and guinea pigs consisted mainly of excessive thickening of the epidermis, with hyperkeratosis and keratotic plugs in the follicular openings. Most of the superficial hair follicles were absent. The sheaths of the remaining deep hair follicles showed a high degree of epithelial hyperplasia with huge nuclei, individual cell keratinization, and large cells containing keratohyalin granules. The hair shafts were absent. Although some of these changes could be ascribed to inflammatory reaction, the

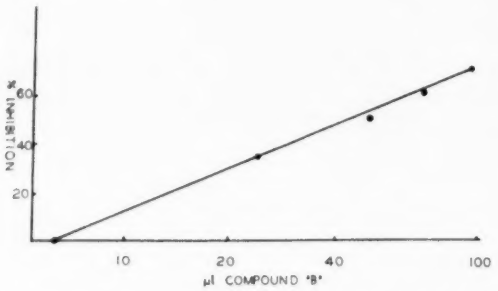

Fig. 5.—Inactivation of —SH groups of glutathione by allyl laurate.

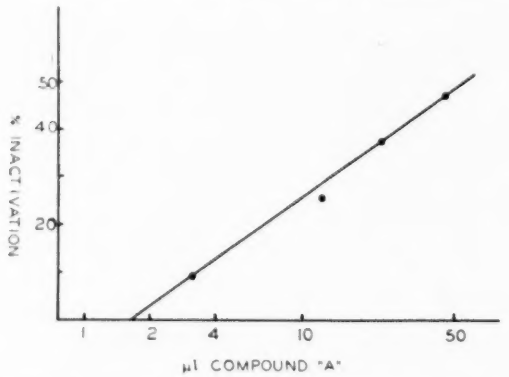

Fig. 6.—Inactivation of free—SH groups in mouse liver homogenate by allyl benzoate in vitro.

absence of an inflammatory cell infiltrate around the hair follicles pointed to a specific action of these compounds on the follicular epithelium (Fig. 4). We were able to confirm the findings of several authors who described the histologic changes in the epidermis following local application of vitamin A.[13] No reference could be found in the literature to the effect of locally applied vitamin A on hair follicles. In our sections of mouse skin treated with vitamin A the sheath cells of the hair follicles were slightly swollen and hyperplastic. The hair shafts disappeared and were replaced by a clump of keratin which was sometimes very dense. However,

13. Studer and Frey.[11b] Sabella, J. D.; Bern, H. A., and Kahn, R. H.: Effect of Locally Applied Vitamin A and Estrogen on Rat Epidermis, Proc. Soc. Exper. Biol. & Med. **76**:499 (March) 1951.

fragments of the hair shafts still remained in the uppermost levels of the hair follicles. The degree of the slight inflammation caused by vitamin A was believed to be too mild to account for the extent of the follicular changes.

The main histologic findings in rabbit skin after treatment with squalene consisted of acanthosis and hyperkeratosis with dilated follicular orifices; these changes developed promptly and extended through the ninth day. The sheath cells of the follicles became swollen by hydropic degeneration beginning on the 5th day; regenerative hyperplasia began on the 10th day and continued for about a week. Most of the hair shafts disappeared at the end of the first week, and only a few coarse hairs persisted. Although the sheath cells began to regenerate on the 10th day, it was not until the 12th day that signs of regrowth of hair were visible. At the end of the second week the shafts were numerous and well formed. No inflammatory reaction could be observed at any stage.

Sections of rabbit skin revealed a small but definite decrease in the free sulfhydryl groups of the epidermis and the follicular epithelium 24 hours after application of squalene, as demonstrated with Bennett's reagent.

In vitro allyl laurate, allyl benzoate, and allyl diphenylacetate inactivated the free sulfhydryl groups of glutathione and of the tissue homogenates tested. The in vitro inhibitory concentrations were considerably higher than those previously reported for the dimer [1] (Figs. 5 and 6). All three compounds inactivated succinic dehydrogenase activity in mouse liver. Approximate concentrations causing 50% inactivation after addition of 0.1 ml. of the allyl compound to 100 mg. tissue were as follows: 50% allyl laurate and 5% allyl benzoate. Under our experimental conditions, allyl diphenylacetate had a slight (about 20%) inhibitory effect only. Larger amounts resulted in complete inhibition. The effect of squalene on —SH compounds in vitro has been described elsewhere.[12]

The in vitro effect of vitamin A was unique among the unsaturated depilatory agents. It had no effect on —SH compounds in vitro, even after preliminary incubation for one hour with liver and skin slices and homogenates. In these experiments, in addition to the in vivo tested preparations, we also used a water-soluble sample of vitamin A ("aquasola," Casimir Funk Laboratories, Inc.).

COMMENT

The finding that a number of nonrelated unsaturated compounds cause reversible baldness supports the theory advanced by us that these compounds owe their depilatory activity to the —C=C— grouping in their molecules. The depilatory action cannot be ascribed to a nonspecific postinflammatory effect, because some of these compounds, such as squalene, cause no inflammation even after repeated topical administration. At present no satisfactory explanation can be offered for the varying susceptibility of various species to different agents. Such variations also have been observed with the dimers of chloroprene.

The question as to whether or not the depilation is due to a reaction between the —C=C— and —SH groups cannot be answered at present. Vitamin A causes hair loss in vivo, but has no effect on —SH compounds in vitro. It is conceivable, however, that a metabolic degradation product of the vitamin is responsible for the interference in the process of keratinization. In this respect it is noteworthy that vitamin A can be considered as a derivative of allyl alcohol. It is also of interest that some unsaturated compounds which had no depilatory effect in mice, such as allyl alcohol, inhibited —SH compounds in vitro. It appears that in vivo other

factors, such as lipoid solubility, boiling point, penetration through the skin, etc., also play a role in determining whether a compound causes hair loss. It should be pointed out that, with the exception of squalene, all in vivo active agents described in this paper may be considered as esters of allyl alcohol. This is of interest in view of the finding that an ester grouping ($-C(=O)-O-C-$) next to the double bond enhances the —SH binding capacity of the unsaturated compound.[3b] This may also explain our observation that allyl diphenylacetate, an ester, causes depilation in vivo, while the isomeric acid is inert. Histochemic evidence has been advanced previously for the inactivation of epidermal sulfhydryl groups by allyl isothiocyanate. It has been also shown that this effect was not due to oxidation of —SH to —S—S—, but probably to a combination between allyl isothiocyanate and the —SH groups of the epidermis.[14] Further chemical work will be necessary before the relation between the depilatory activity and the —SH inactivation can be regarded as uncontroversial. Such work is already in progress.

To the best of our knowledge, the literature contains only one reference about the local effect of allyl compounds on the skin. Hart observed necrosis and sloughing of the skin with frequent lethal outcome after local application of 0.1 ml. of di-(β-methyl-allyl) amine in rats.[15] However, in another publication by the same author, no mention is made of skin changes.[16] Hair loss after local application of vitamin A was described in rats and a porcupine as early as 1938.[5] Previously a number of authors had reported generalized hair loss in animals[17] and in human subjects[18] after oral ingestion of large doses of vitamin A.

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17. Studer and Frey.[11b] Collazo, J. A., and Sanchez, R. J.: Hypervitaminose-A.: Die Symptomatologie der durch Futterung von reinem A-Vitamin an jungen Ratten hervorgerufenen Hypervitaminose-A, Klin. Wchnschr. **12**:1732 (Nov.) 1933. Davies, A. W., and Moore, T.: Vitamin A and Carotene: XI. The Distribution of Vitamin A in the Organs of the Normal and Hypervitaminotic Rat, Biochem. J. **28**:288 (Jan.) 1934. Willstaedt, N.: Die Vitamine: Jetziger Stand ihrer Chemie und Biochemie, Klin. Wchnschr. **14**:841 (June) 1935. Lewis, J. T., and Reti, L.: Sur l'hypervitaminose A et l'innocuité des fortes doses de provitamine A (carotène cristallisé), Compt. rend. Soc. de Biol. **118**:577, 1935. Strauss, K.: Beobachtungen bei Hypervitaminose-A, Beitr. path. Anat. **94**:345 (Dec.) 1934-1935. Weslaw, W.; Wronski, B.; Wroblewski, A., and Wroblewski, B.: Symptomatologie und Verlauf der A-Hypervitaminose bei Ratten infolge enteraler, subcutaner und percutaner Darreichung von Vitamin A Konzentraten: I. Perorale und subcutane Verabreichung des Vitamin A, Klin. Wchnschr. **17**:777 (May) 1938. Baumann, C. A., and Moore, T.: Thyroxine and Hypervitaminosis A, Biochem. J. **33**:1639 (Oct.) 1939. Cornil, L.; Chevallier, A., and Pallas, J. E.: Étude histologique des lésions expérimentales de la survitaminose-A chez le cobaye, Ann. d'anat. path. **16**:74 (Jan.) 1939. Rodahl, K., and Moore, T.: The Vitamin A Content and Toxicity of Bear and Seal Liver, Biochem. J. **37**:166 (Feb.) 1943. Rodahl, K.: Hypervitaminosis-A in the Rat, J. Nutrition **41**:399 (July) 1950.

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In spite of individual variations with different unsaturated compounds, there are certain common features which characterize the action of all local depilatory agents of this group: All of them cause reversible hair loss which is limited to the site of application and is characterized by thickening of the epidermis with anomalies in keratinization and hyperplasia of the hair follicles. The reaction appears to be a common feature resulting from the application of chemically unrelated compounds. Therefore the question must be raised whether it may not also occur in the human skin under pathologic conditions from the excretion onto the skin surface of unsaturated compounds produced within the body. This possibility must be seriously considered in view of the fact that squalene is a normal component of human sebum.[19] A striking confirmation of this theory was found recently by us when we applied human sebum (obtained by ether extraction of the hair of male students or of children) to the skin of mice and rabbits. A single application of human sebum resulted in reversible hair loss in all rabbits and in 5% of the mice tested. Application of commercial wool fat to a control group had no effect. In vitro sebum inactivated free —SH groups and succinic dehydrogenase in dilutions up to 1 : 200. Although these experiments are of a preliminary nature, even at this stage a working theory may be advanced that human sebum may play an important role in disturbances of hair growth and anomalies of keratinization. Detailed data on these experiments will be reported elsewhere.

SUMMARY

Several unsaturated compounds were tested for their local depilatory action in mice, guinea pigs, and rabbits. A single local application of allyl laurate, allyl benzoate, allyl diphenylacetate, and squalene and repeated applications of vitamin A caused reversible hair loss at the site of application.

With the exception of vitamin A, these compounds inactivated in vitro the free sulfhydryl groups of glutathione and of tissue homogenates and the sulfhydryl enzyme succinic dehydrogenase.

It is believed that the —SH-inhibitory effect of these compounds is due to an alkylating reaction between the —C=C— bond and the —SH group.

Local application of human sebum causes reversible hair loss in rabbits and mice.

The theory is advanced that sebum plays an important role in disturbances of hair growth and keratinization.

4526 Locust St.

10 Hillside Road, Claymont.

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COMPARATIVE STUDY OF HISTOLOGY AND CYTOLOGY IN VESICULATING ERUPTIONS

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AND
CARL E. LIPSCHULTZ, M.D.
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DIAGNOSTIC aids are continually being sought in dermatology for making differential diagnoses of vesicular diseases. These aids are especially necessary in the differential diagnosis of chronic pemphigus from bullous erythema multiforme and dermatitis herpetiformis, variola from varicella, varicella from herpes zoster disseminata, herpes zoster from herpes simplex, and erythema multiforme bullosum from various forms of vesiculating dermatitis. The cytologic-smear examination, which at present is popular in the field of diagnostic medicine, was used by us in the study of various vesiculating diseases. In the diagnosis of lymphoblastomata, infectious diseases, such as leprosy and granuloma inguinale, and various neoplastic conditions, such as epitheliomas, tissue smears or imprint studies have frequently been used and reported. These preparations have also been used for the differential diagnosis of vesiculating diseases, with questionable value. We have employed this technique, together with the regular histologic preparations, as a comparative study in some of the more frequently occurring vesiculating eruptions.

METHOD AND MATERIALS

The roof of the vesicle was removed by a scissors or sharp instrument such as a scalpel. In the case of small vesicles, a clean glass slide was firmly applied to the base of the opened lesion, aided by pressure from below by squeezing the lesion manually. For larger vesicles or bullae, the contents of some were aspirated with a syringe, then placed and smeared on a glass slide; others were swabbed with a cotton applicator, then smeared. In all methods, the slides were dried rapidly by fanning to avoid cellular disintegration.

In addition to the smearing technique, a scraping of the vesicle floor was performed with the blade of a scalpel. This was done lightly enough to avoid pain and bleeding. The material thus obtained was spread directly from the scalpel onto the glass slide and quickly waved dry.

At first, the slides of the smears and scrapings were stained with either Giemsa stain, hematoxylin and eosin, or Wright's stain. It was found that, whereas

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From the Division of Dermatology, University of Southern California School of Medicine, and the Los Angeles County Hospital (Medical Unit).

Wright's stain showed cellular elements of blood satisfactorily and the hematoxylin and eosin stain delineated epidermal cellular and fixed-tissue elements well, Giemsa stain outlined all elements well. For this reason, the Giemsa stain was selected for our entire study.

In addition to the above preparation of smears and scrapings of vesicular contents, a similar vesicle from the same patient was excised by a biopsy skin punch under procaine anaesthesia, fixed in 10% formalin, blocked in paraffin, sectioned, and stained with hematoxylin and eosin.

The scalpel-scraping procedure was found unsatisfactory because it was almost impossible to spread the scrapings on the slide evenly. Many of the scrapings were also contaminated with red blood cells and epidermal cells severed from the vesicle wall. It was therefore decided to omit the analysis of scrapings in this study.

Studies were made of 9 patients with herpes zoster, 13 with bullous erythema multiforme, 9 with pemphigus vulgaris, 3 with dermatitis herpetiformis, 19 with vesiculating dermatoses of variable causation, and 3 with epidermolysis bullosa, making a total of 56.

RESULTS

In nine cases of herpes zoster, the histologic picture observed was dependent on the stage of development of the disease. The more recent lesions showed intact, unilocular vesicles with no surface erosion or crusting. The vesicle contents were serum and a few single and multinucleated large epidermal balloon cells. The nuclei of these epidermal cells were large and hyperchromatic. In each cell there was a clear circumnuclear halo. These cells lay on the vesicle floor, free from one another. Underneath the vesicle in the cutis there were areas of hemorrhage and perivascular infiltrate of lymphocytes and polymorphonuclear leucocytes.

In the later stages of the disease, the vesicle roof was intact but crusted. The vesicle floor was composed of a single layer of intact epithelial cells. The contents were primarily polymorphonuclear leucocytes. The single and multinucleated epithelial cells were found not only on the vesicle floor but in all portions of the vesicle, intermingled with the polymorphonuclear leucocytes. In the upper cutis, there was more vascular congestion and hemorrhage than in the early stages, less perivascular, but a more diffuse infiltrate, consisting predominantly of polymorphonuclear leucocytes.

On examination of the smear, regardless of the stage of the disease, large, round cells with basophilic cytoplasm and round hyperchromatic single and multiple nuclei were seen. Keratin fibrils and normal epithelial cells were infrequently observed. Polymorphonuclear leucocytes were numerous in the older lesions.

In 13 cases of bullous erythema multiforme, the histologic section in most instances showed the roof of the vesicle to be full-thickness epidermis and the floor to be the papillary cutis. Occasionally, necrosis of the roof occurred, with replacement of the epidermis by a pus crust. The epidermal pegs adjacent to the vesicle had the appearance of being under tension, since their component cells were lined up with their long axes in a vertical direction, parallel with the presumed tension of the vesicle fluid. These epidermal pegs were also elongated, a further evidence of the vertical tension of the vesicle fluid, which pushed the entire epidermis free from its floor. The papillary cutis, forming the floor of the vesicle, was highly edematous and invaded by nests of varying amounts of polymorphonuclear leucocytes, eosinophils, and lymphocytes. The contents of an early vesicle was serous.

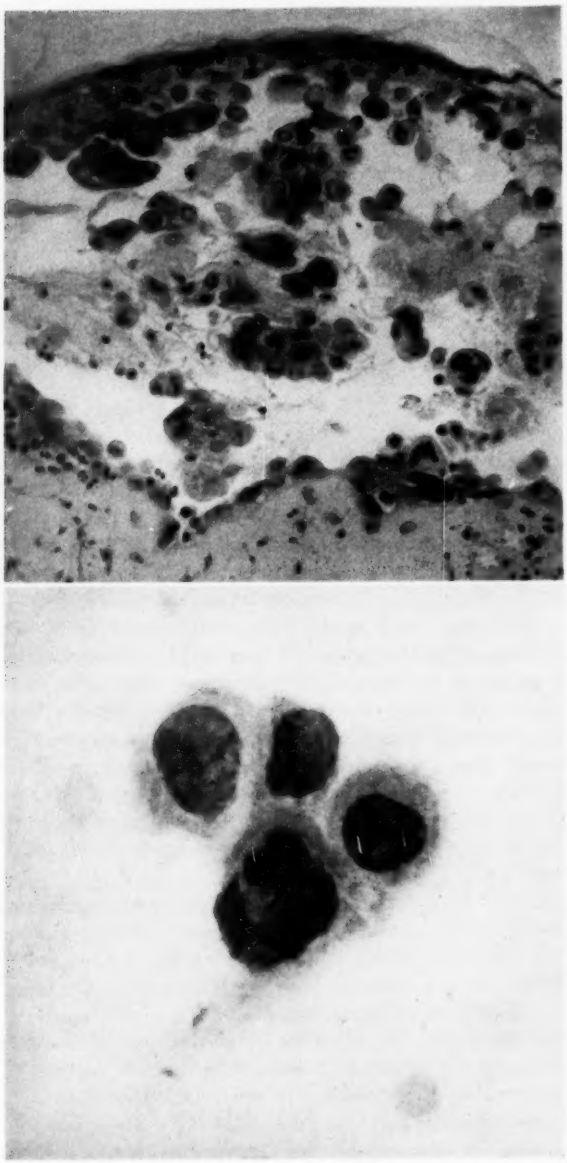

Fig. 1.—Upper, histologic section of herpes zoster vesicle showing lysed epidermal cells and balloon cells; hematoxylin and eosin; × 440. Lower, smear specimen from an early zoster vesicle showing epidermal balloon cells with large hyperchromatic nuclei. A multinucleated balloon cell is also seen; the cytoplasm has lost its prickles and is rounded but still finely granular, like normal cytoplasm; Giemsa; × 950.

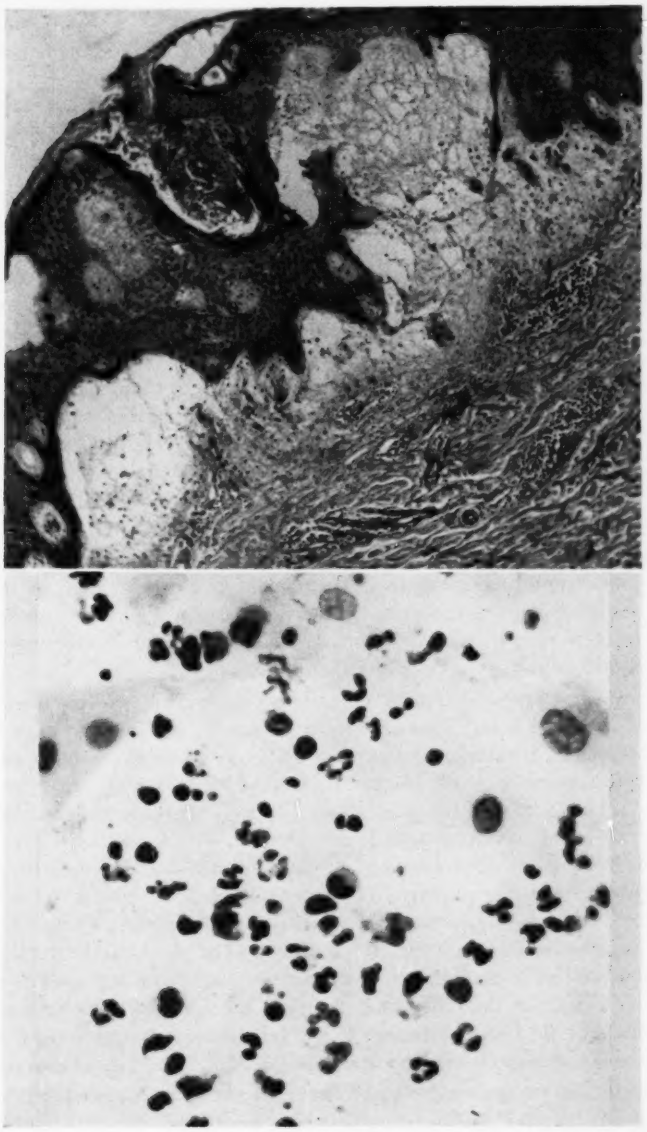

Fig. 2.—Upper, histologic section of an early bullous erythema multiforme showing the subepidermal vesicle and the cellular infiltrate, predominantly polymorphonuclear leucocytes; hematoxylin and eosin; × 100. Lower, smear specimen from an early vesicle of bullous erythema multiforme showing numerous polymorphonuclear leucocytes, a few eosinophils and lymphocytes. In the background are two normal epidermal cells with clear vesicular nuclei and one keratinizing epidermal cell with condensed cytoplasm and a pyknotic nucleus; Giemsa; × 440.

Later, there were degenerated epidermal cells, eosinophils, polymorphonuclear leucocytes, and lymphocytes, in varying proportions.

The smear showed normal epidermal cells, keratin fibrils, polymorphonuclear leucocytes, and eosinophils in varying amounts.

Three cases of dermatitis herpetiformis were observed, one in a Mexican and two in Negroes. All the histologic sections were similar. They showed a primary vesicle and smaller adjacent satellites, all subepidermal and all taller than they were broad. They had, for their roof, epidermis of varying thickness and in various stages of degeneration. The epidermal pegs between and adjacent to the vesicles were elongated, with their component cells in a more or less vertical direction, parallel to the force of the tension exerted by the vesicle fluid. The lateral margins of the vesicle were always rounded. The contents of the vesicles were essentially serous in the upper half and cellular in the lower half. The cellular portion was predominantly eosinophilic, although polymorphonuclear leucocytes, lymphocytes, and red blood cells were numerous. Despite the fact that the cells of the epidermal roof of the vesicle showed vacuolation, these degenerating cells still retained the majority of their pigment. The vesicle floor consisted of cutis invaded by a perivascular infiltrate consisting predominantly of eosinophils but also of polymorphonuclear leucocytes, lymphocytes, and histiocytes. An occasional histiocyte with melanin was seen in the infiltrate.

The smears of the dermatitis herpetiformis vesicles were characterized by dense cellularity, consisting predominantly of eosinophils, as much as 95% ; the remainder were polymorphonuclear leucocytes. Epidermal elements, such as free-lying cells and keratin, were rarely found, but when found showed normal cells with retention of prickles and angulated cellular outline.

Nine patients with pemphigus vulgaris were studied. Seven died of their disease; two are still living. One of the living patients continues to have recurrent eruptions of bullae, after a four-year history. The condition of the other patient has recently transformed into pemphigus foliaceous; she is now critically ill. The histologic section in four of the cases showed entirely subepidermal vesicles. In the remaining five, they were primarily intraepidermal. In two of the slides, the floor of the subepidermal vesicles consisted of papillary cutis which was invaded by a dense infiltrate consisting primarily of eosinophils. In two others, the floor of the vesicle consisted of degenerated, washed-out, subepidermal-basophilic-staining collagen completely devoid of cellular infiltrate. The floor of the intraepidermal vesicles consisted of a single layer of deeply staining, irregular, uneven columnar cells in four cases. In the other case, the floor consisted of three or more layers of epidermal cells. The roof of the vesicle had for the most part an irregular, uneven under surface and was covered by stratum corneum. The lateral margins of the vesicles were slit or knife-edge-like. The epidermal floor rested on a slightly basophilic, degenerated collagen base, which contained congested vessels surrounded by a moderate infiltrate. The latter was predominantly lymphocytic, but also contained a varying number of polymorphonuclear leucocytes and eosinophils at the periphery of the infiltrate.

Interesting was the fact that these vesicles in their earliest stages were much longer in their horizontal than in their vertical axes. The lateral margins seemed to form an acute angle. The cells of the overlying epidermis appeared much like a

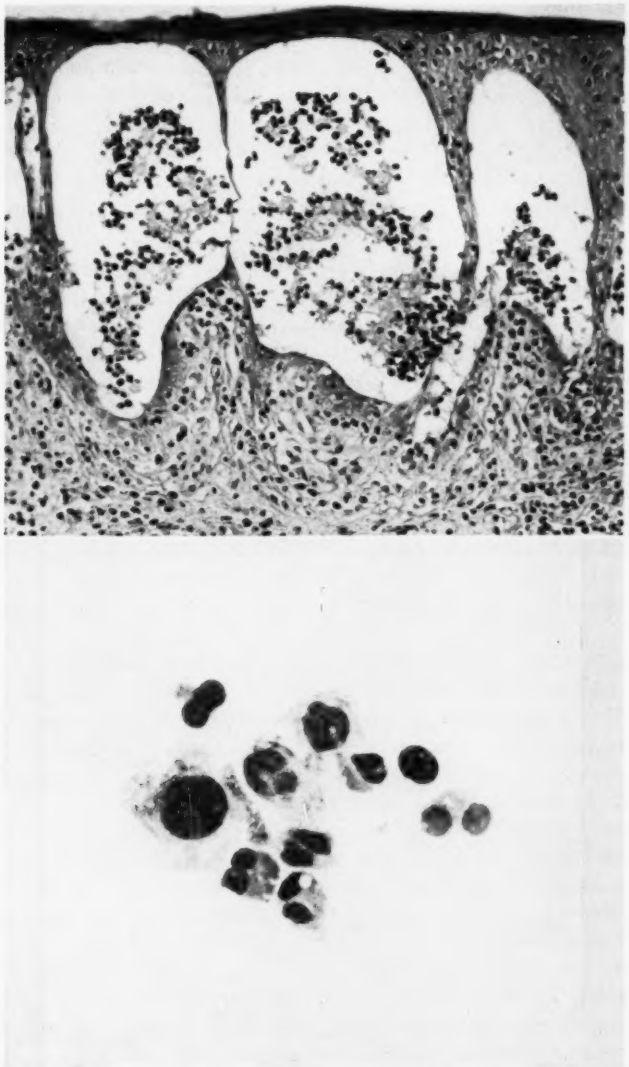

Fig. 3.—Upper, section through a dermatitis herpetiformis vesicle in which the roof is the full-thickness rete of vacuolated cells; the floor is papillary cutis invaded by eosinophils, and the vesicle contents are predominantly eosinophils; satellite vesicles are seen at the periphery; the rounded, lateral borders of the vesicle are characteristic; hematoxylin and eosin; × 100. Lower, smear of dermatitis herpetiformis vesicle showing three normal epidermal cells with round, evenly stained nuclei containing finely granular chromatin. The cytoplasm retains its finely granular consistency and intercellular prickles; the inflammatory cells in this field are seven eosinophils and one lymphocyte; Giemsa; × 950.

syncytium in that the cellular interspaces for the most part were obliterated, and the nuclei of the epidermal roof were still vesicular and appeared to be superimposed on each other.

The contents of the majority of the vesicles were clear and nonstaining in four cases, entirely serous in three, and serocellular in two; the predominating cell in the latter group was the eosinophil. Intermingled with the serous contents, one could see a few eliptical, oval, or rounded free-lying epidermal cells. These cells consisted of normal-sized round nuclei surrounded by normal amounts of amorphous eosinophilic cytoplasm. In some areas these cells could be seen separating from the vesicle wall.

Smears from pemphigus bullae varied uniformly, depending on their location. Those from subepidermal bullae showed an occasional, degenerating epithelial cell, with slight or no keratin fibrils, and varying numbers of polymorphonuclear leucocytes and eosinophils. Smears from the intraepidermal bullae showed numerous epithelial cells in various stages of degeneration, much keratin, an occasional polymorphonuclear leucocyte, and a rare eosinophil. The degenerated epithelial cells were elliptical, oval, or round with round central nuclei and homogenized darker-staining cytoplasm.

Nineteen cases of vesiculating dermatoses were studied. These included 3 cases of Rhus venenata dermatitis, 5 vesiculating id reactions, and 11 cases of histologically nonspecific vesiculating dermatitis. Clinically these nonspecific vesiculating dermatitides consisted of six cases of contact dermatitis due to topical agents or clothing and five cases of vesiculating nummular eczema (vesiculating neurodermatitis).

Histologically the cases of Rhus venenata dermatitis were uniformly similar. Groups of intraepidermal unilocular vesicles, all of approximately the same size, were seen. The stratum corneum was intact over the larger vesicles and fragmented over the smaller vesicles. The stratum granulosum, which was barely perceptible for the most part, was entirely obliterated in the sections showing intense reaction. It had been replaced by round or oval vesicles. The vesicle floor, in the case of larger lesions, consisted of a single layer of compressed epidermal cells. In the rete, which contained microscopic vesicles, diffuse spongiosis was evident, and the epidermal cells were compressed in places by the intercellular edema. This edema was most intense in the upper one-third of the rete, directly below the obliterated zones of stratum granulosum. The basal cells retained their lower most-cytoplasmic wall but not their lateral intercellular walls. The papillary cutis was edematous, and the capillary lumens were narrowed by the edema compressing the vessel walls. In the edematous papillary bodies and in the vesicles one could see an invasion of a large number of eosinophils and lymphocytes, and fewer polymorphonuclear leucocytes. At the lateral edges of the vesicles, the blood vessels were collapsed, but directly beneath the vesicles they were dilated. A dense, perivascular infiltrate of numerous eosinophils in the midst of lymphocytes and polymorphonuclear leucocytes was seen throughout the cutis. Also, many diffusely dispersed eosinophils were seen in the edematous deep cutis.

It was observed that in Rhus venenata dermatitis the smallest vesicles originated in the upper one-third of the epidermis. They were localized directly above the epidermal pegs and not above the papillary bodies in the suprapapillary plates.

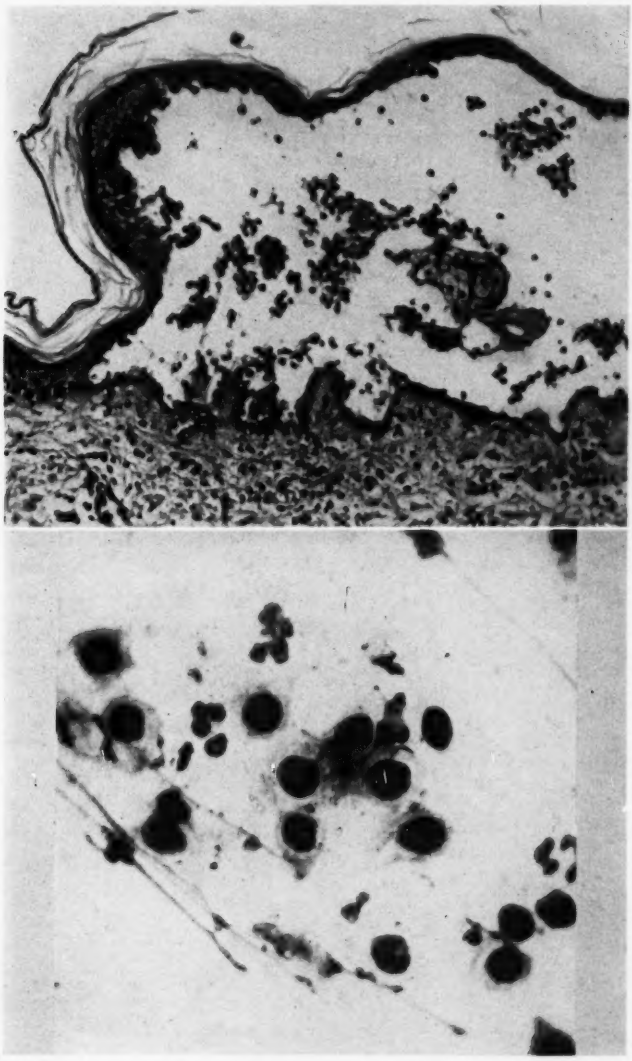

Fig. 4.—Upper, section of a pemphigus vulgaris vesicle, showing the ragged base, lysed nest of sebaceous cells, and other epidermal cells mixed with cellular infiltrate in the intraepidermal vesicle; hematoxylin and eosin; × 100. Lower, smear of pemphigus vulgaris vesicle showing lysed epidermal cells, the nuclei containing irregular stained chromatin, and surrounded by a circumnuclear ring of edema. The cytoplasm is amorphous and rounded off at its periphery; a few polymorphonuclear leucocytes and keratin fibrils are seen between the epidermal cells; Giemsa; × 950.

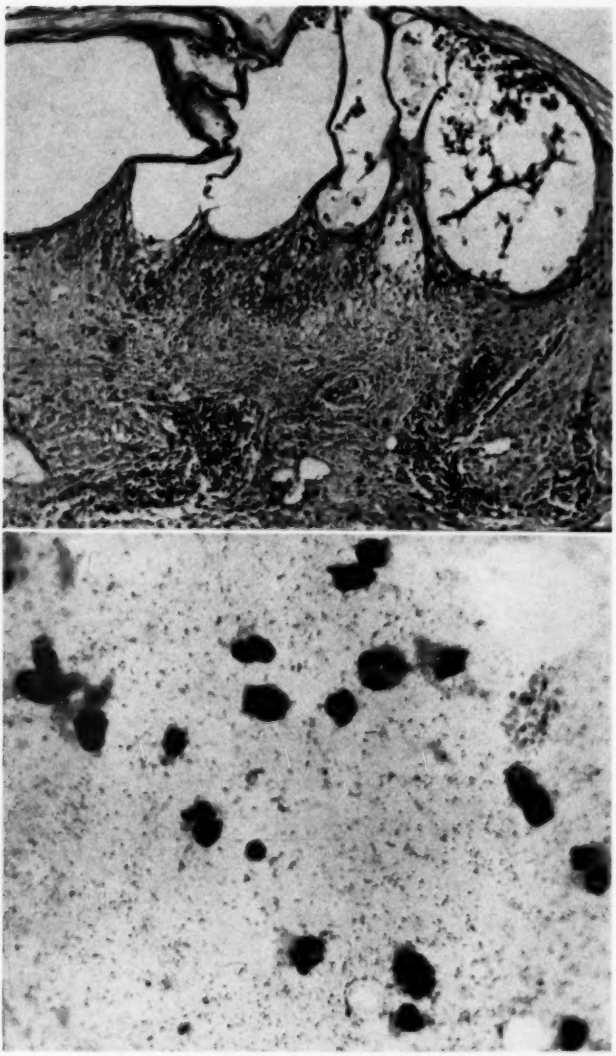

Fig. 5.—Upper, section through a vesicle of Rhus venenata dermatitis, in which the roof is stratum corneum and a thin layer of epidermis; the floor is a single layer or two of epidermal cells. The vesicle contents are clear, serous, and cellular in some areas; heavy perivascular cellular infiltrate in the cutis and in the vesicle floor is predominantly eosinophils; hematoxylin and eosin; × 100. Lower, smear of Rhus venenata vesicle showing 10 eosinophils and 5 polymorphonuclear cells; Giemsa; × 950.

Examination of the smears of the vesicles revealed a uniform absence of epidermal cells and keratin. There was much serum in all three cases. In one no cellular components could be found, in another there was an occasional eosinophil, and in the third there were numerous eosinophils and an occasional lymphocyte.

In sections from the five patients with id reaction, the vesicles were intraepidermal and unilocular. They were oval, wider than tall, and situated more deeply than those of Rhus venenata. The stratum corneum was uniformly intact. The roof and the floor were composed of three to four epidermal-cell layers. The innermost cells lining the vesicle walls were compressed, with their long axes paralleling the contour of the vesicle. The cells of the vesicle floor were edematous and separated from each other by spongiosis. The lateral walls of these cells, rather than their bases, were obliterated by colliquation. Beneath, in the cutis, were congested vessels, as well as a dense, diffuse infiltrate of lymphocytes and polymorphonuclear leucocytes. The cutis was edematous, but retained its normal pink tinctorial characteristics. The center of the vesicle contained granular eosinophilic fragments. At the periphery there were irregular, stellate, amorphous masses simulating fibrin. These masses contained round, pyknotic, single and conglomerate nuclei. The amorphous masses previously described appeared to be suspended from the vesicle walls by stellate threads. The appearance of the vesicular contents suggested a focal necrobiosis.

The predominant findings on the smears were numerous polymorphonuclear leucocytes and epidermal cells. Some of the epidermal cells appeared to be amorphous with their nuclei washed out, undergoing degeneration. A moderate number of keratin fibrils were seen.

There were 11 cases in the group of vesiculating dermatitides. Five of these were diagnosed clinically as vesiculating contact dermatitis because of a definite contact history, and six were diagnosed as nummular eczema because of absence of a known contactant.

Histologic examination of vesiculating contact dermatitis showed intraepidermal, unilocular vesicles whose roofs consisted of stratum corneum and an occasional rete cell. Most of the roof was in a state of disintegration. The floor of the vesicles was composed of one to two layers of epidermal cells. The vesicle contents were of a clear nature, for the most part. At the edge of the vesicle were a few degenerating epidermal cells and keratin, intermingled with a few polymorphonuclear leucocytes. The papillary cutis was edematous and contained a dense, diffuse infiltrate consisting of polymorphonuclear leucocytes, eosinophils, and lymphocytes, which extended up into the epidermal floor of the vesicle. The lower cutis was edematous, as indicated by the increased size of the intrafascicular spaces.

The nummular eczema group, histologically, presented an intraepidermal, unilocular vesicle whose roof consisted of intact stratum corneum and three to four epidermal-cell layers. The floor of the vesicle was composed of three to four layers of intact epidermal cells. The vesicle spaces were clear or contained serum and occasionally a rare epithelial cell. The adjacent epidermis was intact. The papillary and superficial reticular cutis was uninvolved except for perivascular mantles of edema and a slight cellular infiltrate of lymphocytes, plasma cells, and an occasional polymorphonuclear leucocyte.

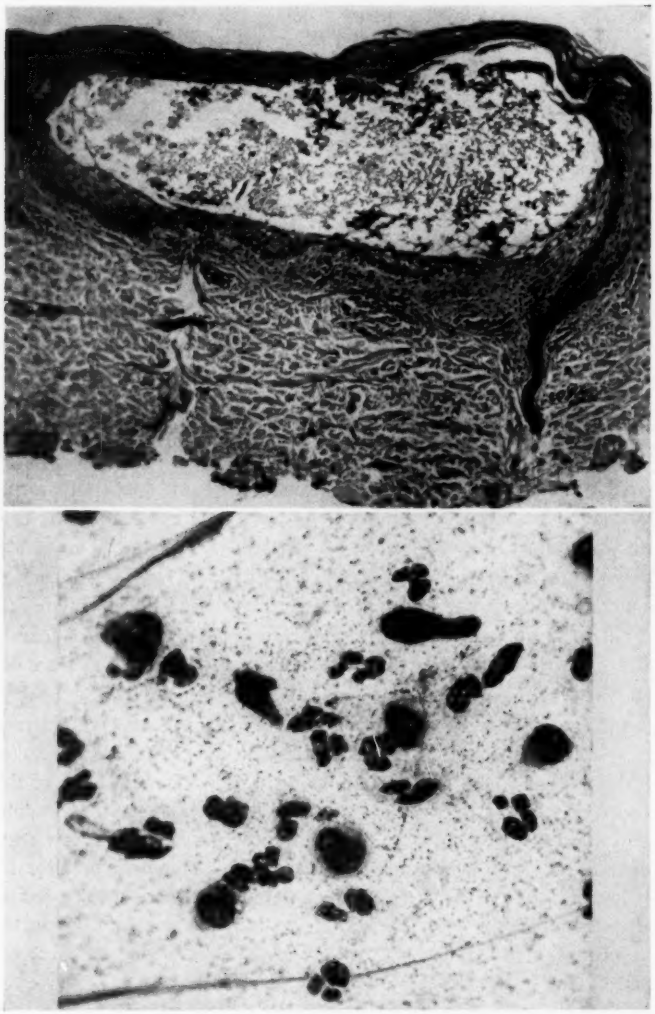

Fig. 6.—Upper, section of a vesicle from id reaction, showing roof consisting of stratum corneum and the floor of epidermal rete; the vesicle contents are degenerated epidermal cells and appear as reticulated fibrils; hematoxylin and eosin; × 65. Lower, smear of id vesicle showing numerous polymorphonuclear leucocytes and a few keratinizing epidermal cells; Giemsa; × 950.

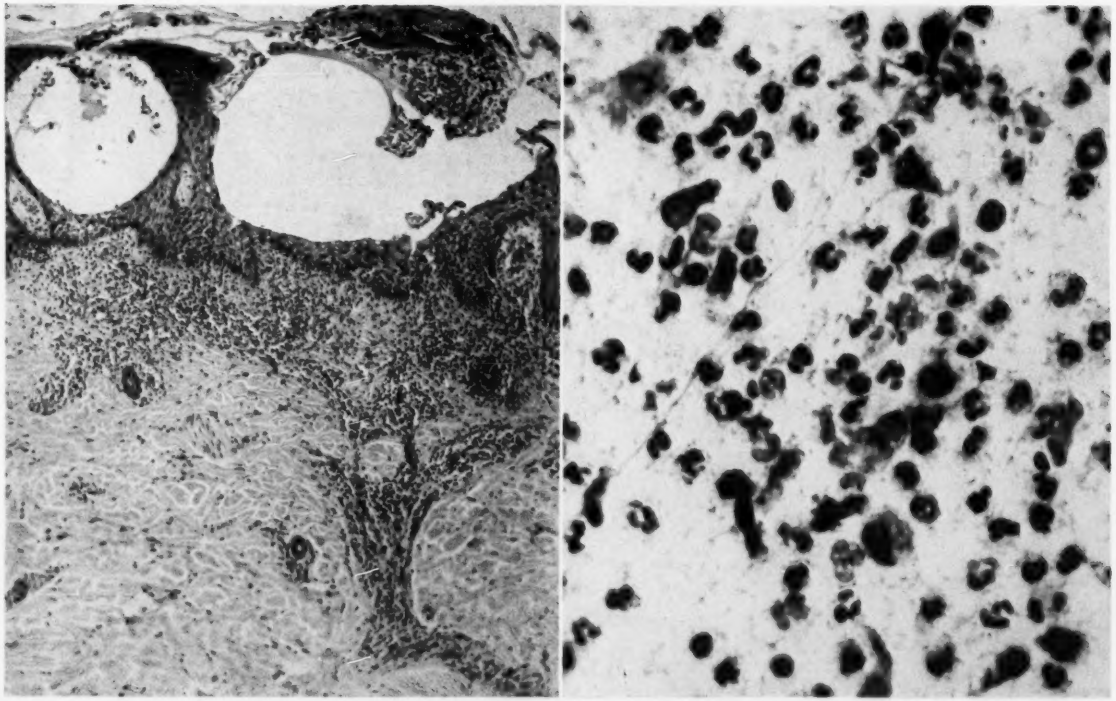

Fig. 7.—Left, section through a vesicle of contact dermatitis, showing the characteristic crusted roof, clear vesicle, thick epidermal floor, and heavy perivascular polymorphonuclear cell infiltrate, diffuse in the upper cutis and perivascular in the lower cutis; hematoxylin and eosin; × 100. Right, smear of a vesicle of contact dermatitis, similar to id eruption, showing numerous polymorphonuclear leucocytes, a few degenerating epidermal cells, and occasional keratin fibrils; Giemsa; × 950.

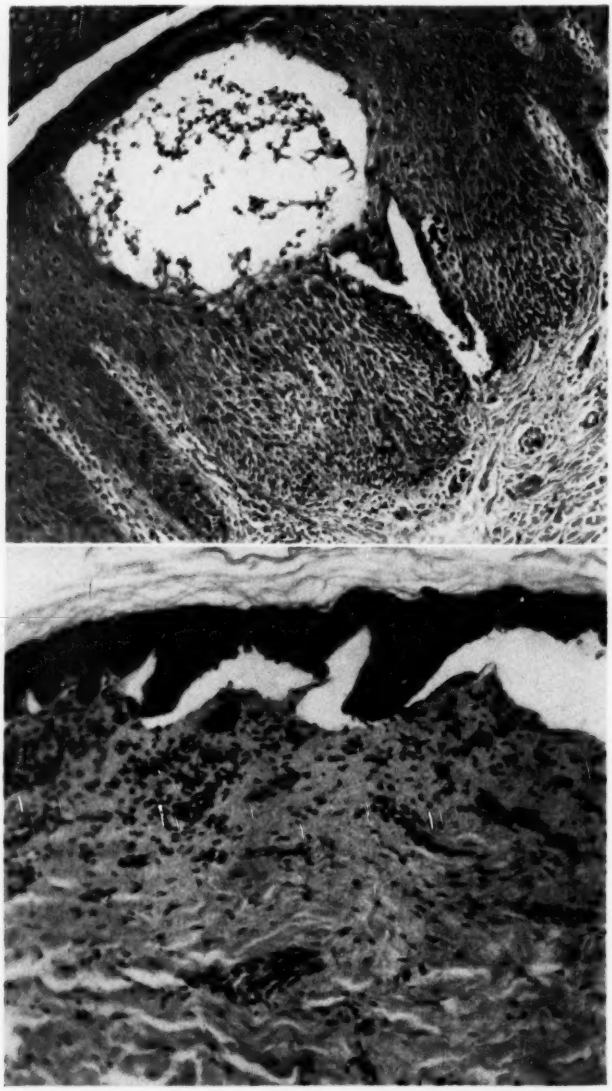

Fig. 8.—Section of a vesicle of nummular eczema showing changes similar to those seen in id reaction; perivascular mantles of edema in the cutis; hematoxylin and eosin; × 100. Lower, section of a vesicle of epidermolysis bullosa with the roof formed by the entire thickness of epidermis with retained epidermal pegs. The floor of papillary cutis has very slight infiltrate; the vesicle, or rather, the split because no contents are evident, is between epidermis and cutis; hematoxylin and eosin; × 100.

The differentiation between vesiculating contact dermatitis and nummular eczema could not, at times, be made clinically. Likewise, the histologic differentiation was impossible at times. In the histologic pattern, however, there were points of slight variation, as is indicated by our foregoing descriptions. In contact dermatitis, prominent features are the relatively superficial location of the vesicles in the epidermis, the disintegrating roof, the cellular invasion of the vesicle floor, the diffuse, dense infiltrate in the upper cutis of polymorphonuclear leucocytes and eosinophils, and the serous, edematous dissociation of the collagen fasciculi in the lower cutis. In the nummular-eczema group the vesicle is relatively deeper, the roof is intact, no cellular invasion of the floor is evident, and perivascular edema,

Comparative Histology and Cytology of Vesiculating Eruptions

Disease *	Location	Edema and Type	Structure	Cavity	Edge and Walls	Cytology of Vesicle Contents
Variola	Intraepidermal	Intracellular, primary?	Reticular epidermal degeneration	Multilocular	Irregular	No cases available for study
Varicella, herpes simplex, herpes zoster	Intraepidermal	Intercellular, primary?	Balloon cells in base of blister	Unilocular	Sharp and irregular	Balloon cells, large hyperchromatic lobulated, irregular single or multiple nuclei; circumnuclear halo
Bullous erythema multiforme	Subepidermal	Pressure primary	Toxic washed-out myxedematous	Unilocular	Rounded and smooth	Epidermal cells, rare polymorphonuclear cells predominate; a few lymphocytes and eosinophils also present
Dermatitis herpetiformis	Subepidermal	Pressure primary	Toxic washed-out collagen	Multilocular satellites	Rounded and smooth	Eosinophils predominate; epidermal cells, if found, have prickles and are normal
Pemphigus vulgaris and foliaceous	Intradermal or subepidermal	Secondary to lysis	Toxic lytic process, many free-lying cells	Unilocular	Sharp and irregular	Degenerated epithelial cells; oval or round pyknotic nuclei with chromatin lumps on nuclear membrane; cytoplasm homogenous; prickles gone
Epidermolysis bullosa	Subepidermal	Secondary	No cells	Unilocular	Sharp and jagged, irregular	No cellular elements in smear
Rhus dermatitis	Intraepidermal	Unilocular *alteration cavitaire*, primary and secondary	Multiseptate pressure, eosinophils	.....	Rounded and smooth	Dense masses of eosinophils; no keratin; no epidermal cells
Id eruption	Intraepidermal	Unilocular *alteration cavitaire*, roof disintegrating	Oval, wider than tall	.....	Rounded and smooth	Much like smears in preceding id eruption

* In contact dermatitis the vesicles are relatively superficial, with disintegrating roof. In nummular eczema the vesicles are deeper, with roof intact and no cellular invasion of floor.

rather than cellular infiltrate, predominates in the upper cutis. The lower cutis has a normal appearance.

Smears of the vesicle contents of all 11 patients were examined at great length. These preparations showed variable amounts of keratin, intact as well as degenerating epidermal cells, lymphocytes, and polymorphonuclear leucocytes in variable numbers. However, no distinguishing characteristics could be observed in smears from either of the two preceding groups of vesiculating dermatitis.

Three patients with the clinical diagnosis of epidermolysis bullosa were studied. The histologic sections showed that the vesicle roof consisted of a full-thickness epidermal rete covered by a relatively thickened, fibrillary stratum corneum. The rete itself was atrophic, but the epidermal pegs were retained, and the cells of the rete appeared normal. The vesicle contents were clear, not cellular or serous. The floor of the vesicle consisted of condensed collagen, which contained amorphous masses of melanin in perivascular chromatophores in the papillary cutis. Numerous

lymphocytes were distributed in the upper cutis. The lower cutis was normal except for the presence of a moderate perivascular lymphocytic and fibroblastic infiltrate. Under the roof of some vesicles, milial cysts containing keratin were observed.

The smears from the vesicles showed primarily serum. However, rare polymorphonuclear leucocytes and lymphocytes were observed, together with a few keratin fibrils; but no recognizable epidermal cells were seen.

COMMENT

Histologic examination has been employed regularly in the study of vesiculating eruptions, especially for purposes of differential diagnosis. Civatte [1] and Lapierre, Van Runckelen, and Dussart [2] have shown that histopathologically pemphigus could be differentiated from dermatitis herpetiformis. Tzanck [3] and, more recently, Rook and Whimster [4] have shown that the cytology of the vesicle fluid is more characteristic for the differentiation of these two eruptions. Tzanck has also found cytologic examination to be of aid in diagnosis of neoplastic diseases. He found that scrapings from basal-cell carcinomas, squamous-cell carcinomas, and malignant melanomas showed cells characteristic of the neoplasm being considered. Tzanck, Sidi, and Melki [5] have recently used the cytologic smear as a diagnostic aid in molluscum contagiosum. They demonstrated anuclear epidermal masses containing irregular, dark-staining granules in smears from a molluscum lesion. More recently [6] they have reported on the cytologic diagnosis of buccal pemphigus vulgaris. Blank [7] has been able to demonstrate mast cells in vesicles of urticaria pigmentosa by cytologic smear. Watson and O'Leary [8] have reported the cytologic examination of the contents of a cantharides blister on patients with acute lupus erythematosus and the finding of Hargraves' L. E. cell.

Vesicles of the skin are formed by several mechanisms. It would naturally follow that vesicle contents would be variable. Vesicles of varicella, herpes zoster, and herpes simplex are characterized by balloon degeneration. This is a lytic process within the epidermis accompanied by intercellular edema. The lysed cells grow in size, forming balloon cells which develop large nuclei and massive cytoplasm. Occasionally, the nuclei divide and form multinucleated balloon cells. These

1. Civatte, A.: Histopathologic Diagnosis of Dermatitis Herpetiformis, Ann. dermat. et syph. **3**:1-30, 1943.

2. Lapierre, S.; Van Runckelen, H., and Dussart, L.: The Value of Histologic Criteria in the Differential Diagnosis Between Pemphigus Vulgaris and Dermatitis Herpetiformis of Duhring-Brocq, Arch. belges dermat. et syph. **2**:81-105, 1946.

3. Tzanck, A.: The Immediate Cytologic Diagnosis in Dermatology, Ann. dermat. et syph. **8**:205-218, 1948.

4. Rook, A. J., and Whimster, J. W.: The Histological Diagnosis of Pemphigus, Brit. J. Dermat. **62**:443-445, 1950.

5. Tzanck, A.; Sidi, E., and Melki, G.: Three Cases of Molluscum Contagiosum with Lymph Node Reaction: Importance of Cytologic Diagnosis, Ann. dermat. et syph. **10**:263-268, 1950.

6. Tzanck, A.; Sidi, E.; Melki, G., and Damorseau: Immediate Cytologic Diagnosis in a Case of Subacute, Malignant, Extensive Pemphigus of the Buccal Area, Bull. Soc. franç. dermat. et syph. **57**:388-389, 1950.

7. Blank, H.: To be published. Shelly, W. B.: Personal communication to the authors, 1950.

8. Watson, J. B.; O'Leary, P. A., and Hargraves, M. M.: Neutrophils Resembling L. E. Cells in Artificial Blisters, Arch. Dermat. & Syph. **63**:328-333 (March) 1951. O'Leary, P. A.: Personal communication to the authors.

balloon cells appear not unlike cancerous epithelial cells seen in cytologic smears of neoplasms. Although the prickles are gone and the cells have rounded borders, the nuclei and the cytoplasm stain normally, indicating cells are of normal viability. These characteristic balloon cells can be found easily in the cytologic smear preparation of a clear, intact vesicle before macroscopic pus formation has occurred.

In the vesicles of pemphigus, which histologically are characterized by a roughened interior, free-lying, lysed cells, and narrow angulated lateral margins, the smears showed epidermal cells of normal size, but with shrunken nuclei and nuclear

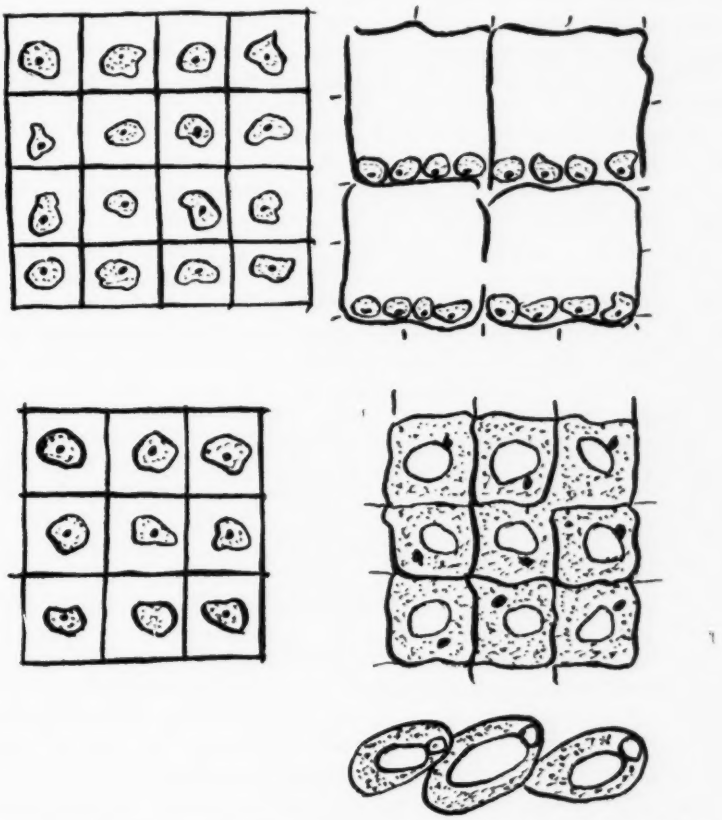

Fig. 9.—Upper, balloon degeneration. Interspaces enlarge, and there is intercellular edema. Nucleated cells fall to base, and unilocular vesicle forms. Lower, intracellular reticular degeneration. Reticulum around cell remains; nuclei are ejected; protoplasm forms multilocular vesicles.

chromatin in irregular clumps. The cytoplasm was condensed at the periphery of the cell and stained much darker. A definite contrast was the narrow band of circumnuclear vacuolation. These toxic manifestations of the lysed cells in the smear of a pemphigus bulla correspond to the toxic appearance which has been observed by histopathologists in the basophilic staining of the collagen in the upper cutis as well as in the epidermal cells of the histologic section of pemphigus vulgaris.

In dermatitis herpetiformis, the subepidermal vesicles, with their content of eosinophils and other inflammatory cells, the rounded lateral vesicle margins, and the satellite arrangement of subepidermal vesicles have been considered characteristic histologically for many years. The cytology of the vesicle fluid is likewise distinctive in that it shows normal-appearing epidermal cells with irregularly shaped cell borders. Because of the absence of lysis these cells are mechanically torn from their neighbors. Our smears also showed bundles or masses of such epidermal cells surrounded by numerous eosinophils.

Bullous erythema multiforme is characterized histologically by intense pressure (or separation) and subepidermal vesicle formation, much as is seen in dermatitis herpetiformis. There are elongated rete pegs in parallel arrangement, which are apparently under great tension. Strands of degenerating collagen connecting the vesicle roof with the floor are evident. The lysis here is physiologically different from that in dermatitis herpetiformis and may represent more of a toxic process than an allergic one. The smears in bullous erythema multiforme showed a predominance of polymorphonuclear leucocytes, a smaller number of lymphocytes, an occasional eosinophil, keratin fibrils, and normal epidermal cells.

Epidermolysis bullosa, histologically, showed separation of the epidermis from the cutis, but no free-lying cells within the cavity of the vesicle. The smear showed only an occasional, normal epidermal cell and no infiltrating cellular elements. The site of lysis in the epidermolysis bullosa is localized to the same zone as the site of lysis in dermatitis herpetiformis. Its difference is the extreme paucity of cellular elements. The occasional epidermal cells which are present in the smears, however, are normal.

From this study we can separate the early lesions of the vesiculating diseases which are caused by lysis into two categories: (1) lysis of the epidermal cells themselves in varicella, herpes zoster, herpes simplex, and pemphigus, and (2) lysis of the epidermis from the cutis in dermatitis herpetiformis, bullous erythema multiforme, and epidermolysis bullosa. In the second group the epidermal cells may be compressed by the intercellular edema, but they appear normal and cohere to each other.

Because of the intense cellular lysis, the blisters of herpes zoster and pemphigus are easily ruptured by mild pressure. In variola there is little lysis, and a blister is ruptured by external pressure with great difficulty. The same can be said with reference to the rupturing of lesions of other blister-forming diseases which do not have lytic properties, such as the vesiculating dermatoses.

The three groups of vesiculating dermatoses studied were Rhus dermatitis, id eruptions, and a category which comprises contact dermatitis and so-called nummular eczema.

In Rhus dermatitis, the characteristic lesion is an intact, large, intraepidermal vesicle with serous contents and a predominantly eosinophilic infiltrate in the upper cutis. The vesicle smear presented no epidermal elements but showed numerous eosinophils. In this subgroup of vesiculating dermatoses, both histologic and cytologic examinations are distinctive.

Histologic section of an id eruption showed an intact vesicle in the midepidermis and moderate polymorphonuclear leucocytic and lymphocytic infiltrate in the cutis.

This could be distinguished from Rhus and contact dermatitis, but not from nummular eczema. The cytologic examination, although showing large numbers of normal and distintegrating polymorphonuclear leucocytes and epidermal cells, was not considered definitive enough to be of diagnostic aid.

Contact dermatitis sections showed vesicles in the upper epidermis. The roof of the vesicle was formed by serous crusts, the floor by epidermis invaded by a pleomorphous cell infiltrate. The histopathologic pattern was characteristic and could readily be differentiated from that of Rhus venenata dermatitis and the id eruptions. The cytologic smear was distinctive, and by the absence of great numbers of eosinophils it could be differentiated from Rhus venenata dermatitis.

Nummular eczema, histologically, with its usually intact vesicle in the middle or upper epidermis, slight cellular infiltrate, and perivascular mantles of edema, could be sufficiently distinguished from contact dermatitis and the id eruptions. It was not possible to make a cytologic differentiation of nummular eczema from id vesicles or contact dermatitis on the basis of vesicle content, but again absence of eosinophils differentiated it from Rhus venenata dermatitis.

SUMMARY

Histologically and cytologically we were able to differentiate herpes zoster, pemphigus vulgaris, dermatitis herpetiformis, Rhus venenata dermatitis, epidermolysis bullosa, and bullous erythema multiforme. The histopathologic pattern was definitely diagnostic in the great majority of these conditions. When it was doubtful or questionable, the cytologic examination was not only supportive but also, at times, diagnostic. Finding of balloon cells was indicative that the disease was varicella, herpes zoster, or herpes simplex. (One must not lose sight of the fact that herpes of the genital tract could present balloon cells which might result in a misdiagnosis of cancer.) The demonstration in the cytologic smear of toxic, rounded, epidermal cells with amorphous pyknotic nuclei was indicative of pemphigus vulgaris. Clumps of normal epidermal cells with heavy eosinophilia were distinctive of dermatitis herpetiformis. The finding of few or no cellular elements or epidermal cells was characteristic of epidermolysis bullosa. The histologic pattern of bullous erythema multiforme was more diagnostic than the smear. To differentiate bullous erythema multiforme from dermatitis herpetiformis or pemphigus vulgaris, however, the cytologic examination can be a very valuable aid. The finding of numerous eosinophils and almost complete absence of epidermal cells was distinctive of Rhus venenata dermatitis.

Contact dermatitis, nummular eczema, and the id eruptions could not be differentiated cytologically from one another.

CONCLUSION

The cytologic study of smears from blisters of 56 patients with vesiculating eruptions offers a valuable aid to histopathologic examination and to differential diagnosis of vesiculating diseases.

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Avis Gregersen assisted in preparation of the cytologic and histologic slides, and Lloyd Matlovsky made the photomicrographs.

ABSTRACT OF DISCUSSION

DR. HERMAN BEERMAN, Philadelphia: We are indebted to Dr. Winer and Dr. Lipschultz for a careful comparative study of the histologic and cytologic findings of certain vesicular and bullous diseases. They found the histopathologic pattern definitely diagnostic in a majority of the processes studied, and in cases with microscopic features of questionable diagnostic value the cytologic examination at times settled the issue. Thus, Dr. Winer, who has for a long time been interested in methods supplementary to ordinary histopathologic techniques, has demonstrated that a new procedure may be a useful aid in differentiation of certain disease processes which are a real problem in clinical practice. Ordinarily, one has little difficulty in clinical differentiation of the acute vesicular dermatitic reactions. The chief trouble lies in distinguishing between pemphigus, dermatitis herpetiformis, and erythema multiforme.

Until recently most dermatopathologists have contended that the bulla of pemphigus has no diagnostic histologic appearance and cannot with certainty be differentiated from the bulla of dermatitis herpetiformis. Civatte in 1943, however, claimed that the histopathology of pemphigus is distinctive and that its differentiation from dermatitis herpetiformis and erythema multiforme is possible. He found the primary change in pemphigus to be in the epidermis, and at certain areas he noted epidermal cells which had lost their prickles and were thus separated from their neighboring cells, a process called acantholysis. As a result of this acantholysis, clefts developed in the epidermis, usually between the basal layer and the rest of the epidermis. Enlargement of these clefts led to bulla formation along with detachment of a single cell or clusters of cells without intercellular bridges, and additional signs of degeneration, swollen nuclei, and homogenization of the cytoplasm, which produced cells resembling the balloon cells of herpes zoster. These acantholytic cells were found in pemphigus vulgaris, pemphigus foliaceus, and pemphigus vegetans, but not in dermatitis herpetiformis. In addition to the cytologic changes, Civatte maintained that the bullae of dermatitis herpetiformis and erythema multiforme were subepidermal.

Butcher's pemphigus (acute infectious bullous dermatitis), likewise, was subepidermal and is not considered by Civatte to be related to the other three types of pemphigus. Lapierre, Van Runckelen, and Dussart found similar changes in pemphigus and dermatitis herpetiformis. Cordero and others, and Dupont and Pierard also attested to the belief that pemphigus was epidermal and dermatitis herpetiformis was subepidermal. In the past four years Tzanck and his colleagues have proposed a cytologic test in which scrapings taken from the floor of bullae are spread on a slide and stained with Giemsa's stain. In pemphigus there are swollen round or oval epidermal cells devoid of intercellular bridges. In dermatitis herpetiformis only inflammatory cells are present. Rook and Whimster have confirmed the findings of the French and Belgian schools, both as to the histologic appearances and as to the value of the cytologic findings.

Lever, who has permitted me to see his forthcoming comprehensive study, has also brought convincing evidence of the value of histologic examination in determining the type of pemphigus present. On the other hand, in a carefully conceived and executed study, Percival and Hannay examined serial sections of bullae from cases of dermatitis herpetiformis, pemphigus, and erythema multiforme, and showed that in all cases the bullae are subepidermal in origin. Regeneration of epithelium may occur on the dermal floor of bullae and give the impression that the lesions are intraepidermal. They felt that their findings invalidated the Tzanck test for differentiating between pemphigus and dermatitis herpetiformis.

There are, therefore, two problems: first, whether there is a distinctive histologic picture in pemphigus versus dermatitis herpetiformis, and second, whether the Tzanck test is of value. With regard to the distinctive histologic picture of pemphigus, I can show that acantholysis may occur in more than pemphigus, for example, in Hailey and Hailey's disease or so-called benign familial pemphigus, in congenital ichthyosiform erythroderma, in senile keratosis, and in cancer. Thus, one must interpret the histologic findings, even though present in more than one process, in conjunction with the clinical aspects of the case. Lever did this in his study and confirmed the claim for specificity of the pathologic picture in pemphigus. In this connection Rook, in a personal communication, has supplied me with data which would also tend to reconcile the apparently divergent points of view:

"We were so impressed by the divergence of our views that Whimster and I spent some time going through Percival's material. We found that he had no sections showing the

histological picture we considered diagnostic of pemphigus, except in his cases of pemphigus foliaceus. The cases which he had labeled pemphigus vulgaris were of the type which we, following Goodman, called senile dermatitis herpetiformis. I understand that Percival has since had a true case of pemphigus vulgaris showing acantholysis. Our differences of opinion would, therefore, seem to be due to the relatively greater rarity of pemphigus vulgaris in Scotland. This may just possibly be attributable to the very small number of Jews in Edinburgh. Since I came down to Wales six months ago I have seen only one case of true pemphigus, but I have seen four cases of pemphigoid dermatitis herpetiformis. I am satisfied that the whole group of bullous eruptions comprised by the terms pemphigus and dermatitis herpetiformis, or better, the wider term, dermatitis polymorphes bulleuses of Brocq, needs to be reviewed according to histological criteria."

When this is done, Rook stated, two main groups emerge: One is the pemphigus group which includes pemphigus vulgaris, pemphigus erythematosus, pemphigus vegetans, pemphigus foliaceus. Despite minor differences, all these conditions, which are probably merely phases of the same condition, show the same basic histologic picture. The other group is the dermatitis herpetiformis group, including Duhring's disease, senile dermatitis herpetiformis as described by Goodman, various localized bullous eruptions which should be differentiated from the primary lesion of pemphigus, and certain conditions of the type described as benign pemphigus by Brocq.

With regard to the usefulness of the Tzanck test, Blank and Burgoon of the University of Pennsylvania have collected data which indicate that this test is of great value for diagnosis of pemphigus.

In short, as Dr. Winer and Dr. Lipschultz have shown, properly interpreted histopathologic changes in the bullous dermatoses, supplemented by cytologic and clinical studies, afford a reasonable basis for their positive differentiation.

DR. CARL W. LAYMON, Minneapolis: I had several points to discuss about this paper, but Dr. Beerman covered most of them. Dr. Winer's slides pictured his subject beautifully. The cytologic studies of smears from bullae and vesicles were most interesting to me. Dr. Beerman brought out the difficulties in differential diagnosis between pemphigus, dermatitis herpetiformis, and erythema multiforme. I believe perhaps the most difficult differential diagnosis is between borderline cases of dermatosis herpetiformis and pemphigus, and if we had even one reliable method which would enable us to make such a differential diagnosis it would be a great advance.

When we consider the so-called clinical aids, such as the degree of eosinophilia in blister fluid and blood, grouping or lack of grouping of the lesions, the sensitivity to the halogens, etc., not one is infallible. As Dr. Winer pointed out, Tzanck felt that scrapings from blister fluid were a great help in differential diagnosis. Other workers, however, are not so enthusiastic. More work along this line has to be done in order to further clarify the problem. Dr. Winer's studies are to be highly commended.

DR. FRANCIS A. ELLIS, Baltimore: Dr. Winer has presented a clear and concise picture of these various dermatoses. We have not used this particular test to any extent, and I do not know of any reports of the difference between the contents of the bullae and taking the top off and scraping the base. Since we are dealing with nuclei, perhaps special nuclear stains may be of more value than the routine stains now used.

We are especially interested in the Tzanck cell in which the nucleus becomes deeper stained with a dense rim of eosinophilic cytoplasm. Because this type of cell is seen in so-called benign familial pemphigus, I suggested the possibility that it might be a "pre-corp-rond." This certainly deserves more study. I would like to have the investigators who are familiar with the test, if they have an opportunity, examine the tissue from so-called benign familial pemphigus to see if these Tzanck cells are present or if the "pre-corp-rond" cell can be differentiated from the Tzanck cell of pemphigus vulgaris.

This type of test should be of value in differentiating conditions which were originally called the varicelliform eruptions, eczema vaccinata and generalized herpetic eruption. By a simple smear from the lesions one should be able to differentiate these two diseases if one sees the lesions at the proper stage.

DR. L. H. WINER, Beverly Hills, Calif.: I wish to thank the discussors, especially Dr. Beerman, for their kindness and constructive criticism. I had hoped that Dr. Ellis would mention the fact that epitrichial cells are the cells which appear to be the free-lying cells in Hailey and Hailey's disease, or benign familial pemphigus. It is a hereditary retention of epitrichial cells.

Malignant cells in epithelium undergo lysis. Malignant melanomas and adenocarcinomas also undergo liquefaction degeneration, producing cavities. Tzanck, in his original work, studied smears of both prickle- and basal-cell carcinomas, as well as melanomas. He showed that prickle-cell carcinoma and melanoma could be identified by free-lying or lysed malignant cells, whereas the basal cells were massed.

I wish to reemphasize Dr. Laymon's statement that this procedure is not simple. It is not a procedure for an amateur, but one which requires cytologic study, as do the present-day cytologic examinations of smears from the vagina for cancer of the uterus, etc. Carcinoma cells in the sputum are missed by the uninitiated. Therefore, one must spend time to acquaint oneself with the normal as well as the abnormal cells in these smears.

Borderline cases of dermatitis herpetiformis and pemphigus can always be difficult to differentiate. This test offers us an aid to proper diagnosis.

Dr. M. S. Buerk and Dr. H. Blank (*New England M. J.* **244**:670-672, 1951) have demonstrated balloon cells in Kaposi's varicelliform eruption or disseminated herpes simplex, indicating that this disease belongs to the herpes varicella group, rather than to the erythema multiforme group.

CORRELATION OF EMOTIONAL STATUS AND REACTIVITY TO CUTANEOUS STIMULI IN FUNCTIONAL DERMATOSES

MAXIMILIAN E. OBERMAYER, M.D.

In Collaboration with Robert Blair, M.D.; C. Fiske, B.A.; Harry Levitt, M.D.; Stephen Rush, B.A., and Margaret Ann Storkan, M.D.; with the Technical Assistance of Ellen Glenn, R.N.

LOS ANGELES

BECAUSE of the prevalent interest in psychosomatic relations, it seemed both interesting and worth while to attempt to establish or disprove the existence of a relation between emotional status and reactivity to cutaneous stimuli of patients with functional dermatoses.

Psychiatric studies of patients with cutaneous disease have been done by a great many workers with widely varying spheres of experience, including dermatologists, allergists, psychologists, psychiatrists, and psychoanalysts. Valuable data have been accumulated. Among recent studies are Cormia's [1] detailed observations on patients with diverse dermatoses and Williams' [2] work on maternal rejection. Subjective clinical impressions, as we know from our own experiences, are not necessarily accurate, and the greatest defect of the many reported studies has been their subjectivity.

In order to attain a greater degree of objectivity in establishing the patient's emotional status and to achieve standardized data, we decided to employ projective tests. The results of such tests are superior to those attained by direct questioning, which elicits only material of which the patient is aware, because they give information about the subconscious realm of the personality. Menninger [3] has pointed out that projective techniques are valuable diagnostic aids because they can reveal incipient mental disease earlier than purely psychiatric studies.

There are a great many projective tests. That some delve more deeply into the structure of the patient's personality is illustrated by the schematic representation in Figure 1. Direct questioning, the airplane flying above the water, does not "dip" into the subconscious. Such techniques as the thematic apperception test, the ship,

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From the Department of Dermatology, University of Southern California School of Medicine, and Veterans' Administration Hospital, Long Beach, California.

1. Cormia, F. E.: The Role of Psychosomatic Factors in Dermatoses, Connecticut M. J. **14**:1051 (Dec.) 1950; Basic Concepts in the Production and Management of the Psychosomatic Dermatoses, Brit. J. Dermat. **63**:83 (March) 1951.

2. Williams, D. H.: Management of Atopic Dermatitis in Children: Control of the Maternal Rejection Factor, A. M. A. Arch. Dermat. & Syph. **63**:545 (May) 1951.

3. Menninger, K.; Rapaport, D., and Schafer, R.: New Role of Psychological Testing in Psychiatry, Am. J. Psychol. **103**:473 (Jan.) 1947.

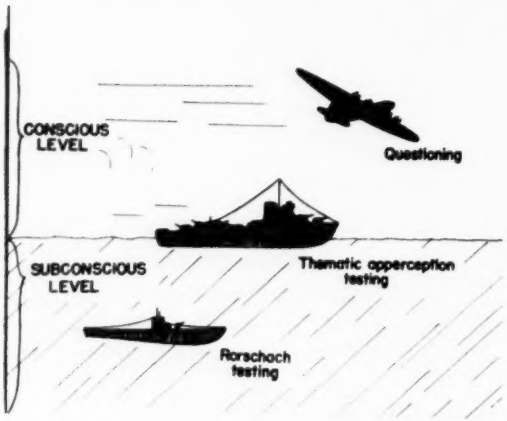

Fig. 1.—Schematic representation of projective tests.

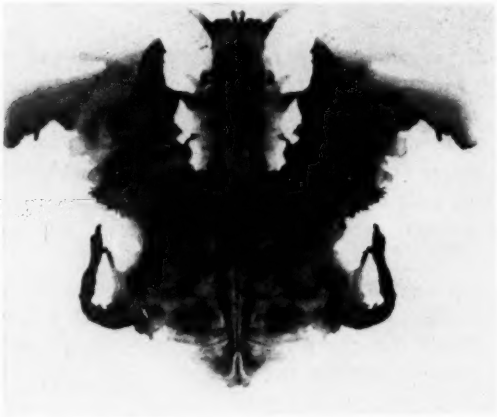

Fig. 2.—Sample of Rorschach test card.

Fig. 3.—Sample of thematic apperception test card.

elicit information from both the conscious and the subconscious sphere. A test such as the Rorschach, the submarine, explores the lowest levels of the patient's subconscious mind.

METHOD

We chose for the purposes of this study the Rorschach, thematic apperception, word association, draw-a-person, and Otis intelligence tests. A combination of several tests rather than a single one was selected because a more rounded picture of the patient's total personality is attained by a variety of techniques.

In the Rorschach test the patient's responses to a series of fuzzy, amorphous ink blots, both black and colored, are recorded (Fig. 2). In the thematic apperception test (T. A. T.) a set of picture cards (Fig. 3) representing a variety of scenes and

TABLE 1.—*Sample of Word Association Test*

No.	Stimulus	Reaction	Time, Sec.	Recall	Time, Sec.
1	World	Oceans	5	Same	⅕
2	Love	Hate	2	Same	2
3	Father	Mother	½	Same	½
4	Hat	Coat	1	Father	2
5	Breast	Milk	4	Nipple	3
	etc.				

TABLE 2.—*Sample of Otis Intelligence Test*

Examination begins here:

1. The opposite of hate is (?)
   1 enemy, 2 fear, 3 love, 4 friend, 5 joy.....
2. If 3 pencils cost 5 cents, how many pencils can be bought for 50 cents?.....
3. A bird does not always have (?)
   1 wings, 2 eyes, 3 feet, 4 a nest, 5 a bill.....
4. The opposite of honor is (?)
   1 glory, 2 disgrace, 3 cowardice, 4 fear, 5 defeat.....
5. A fox most resembles a (?)
   1 wolf, 2 goat, 3 pig, 4 tiger, 5 cat.....

situations involving persons of both sexes and varying ages is shown to the subject, who is told to relate a story suggested by the picture and to include a description of the emotions and thoughts of the characters. The word association test (Table 1) employs a series of familiar words. The subject is instructed to respond as quickly as possible, when shown each word, with the first word which crosses his mind. A second exposure to the same set of words, known as the recall, is used to check the consistency of his responses. In the draw-a-person test the subject is asked to sketch a "whole" human figure and when this is completed to draw a person of the opposite sex (Fig. 4). A portion of the Otis intelligence test, one of the best known of the many devices for measuring the adaptive use of the subject's capacities, is shown in Table 2.

The time consumed by the two psychologists who cooperated in this study in giving, scoring, and interpreting the set of tests was about eight hours per subject. In addition some of the patients were examined by psychiatrists.

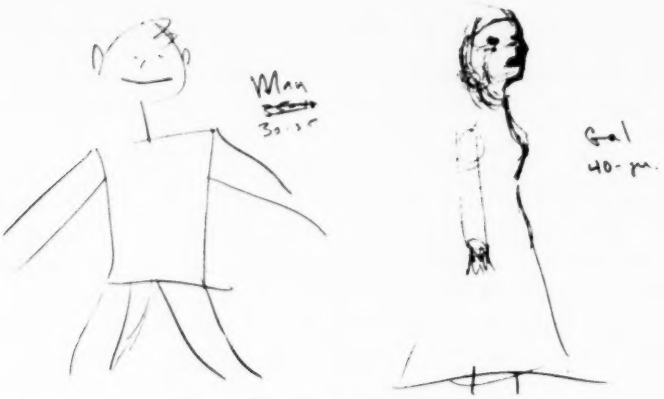

Fig. 4.—Sample of draw-a-man test.

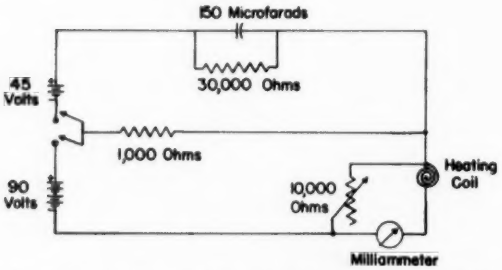

Fig. 5.—Pain threshold meter, designed by George Mount, Ph.D.

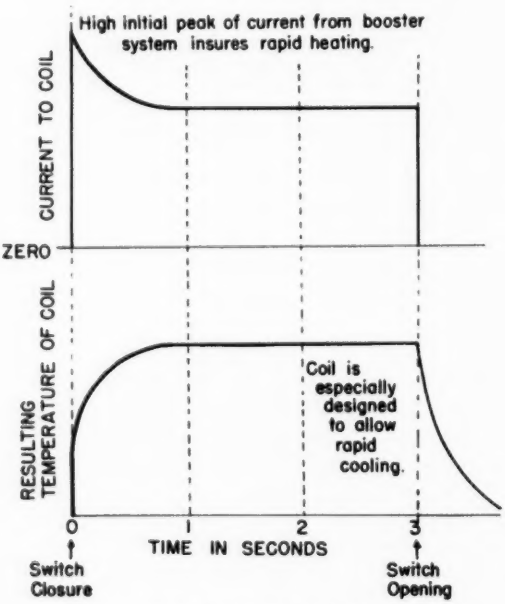

Fig. 6.—The Mount pain threshold meter.

After considering the many methods available for studying reactivity to cutaneous stimuli, we decided to use two procedures: The first establishes the reaction to histamine, introduced by iontophoresis, and the second, the threshold of pain, determined by a specially designed instrument.

Pieces of filter paper 1 cm. square, saturated with a solution of histamine phosphate, 1 : 1,000, were placed on the subject's back and covered by a metal cylinder weighing 420 gm., which served as the negative pole. A galvanic current of 2 ma. was allowed to flow for six specified periods, that is, 5, 10, 15, 20, 25, and 30

TABLE 3.—*Data About Patients*

No.	Name	Sex	Age, Yr.	Coloration		Occupation	Diagnosis	Duration of Disease, Yr.
				Hair	Eyes			
1	C. B.	M	34	Brown	Blue	.....	Neurodermatitis	9
2	C. M.	M	36	Brown	Blue	Grocery clerk	Neurodermatitis	6
3	F. O.	M	38	Black	Brown	Bar tender	Neurodermatitis	9
4	R. K.	M	30	Brown	Brown	Clerk	Neurodermatitis	8
5	W. W.	M	50	.....	.....	Carpenter-Plumber	Neurodermatitis	5
6	J. G.	M	64	Bald	Blue	Elephant trainer	Neurodermatitis	22
7	M. C.	M	41	Brown	Blue	Taxi driver	Pruritus ani	1
8	A. D.	M	57	.....	.....	Cook	Neurodermatitis	30
9	B. S.	F	23	Brown	Blue	Clerk	Neurodermatitis	23
10	R. P.	M	23	Brown	Blue	Engineer	Neurodermatitis	23
11	W. A.	M	25	Brown	Blue	Accountant	Neurodermatitis	6
12	R. W.	M	23	Brown	Blue	Accountant-Carpenter	Neurodermatitis	10
13	R. S.	M	24	Blond	Blue	Athletic coach	Neurodermatitis	6
14	M. L.	F	28	Blond	Blue	Psychologist	Neurodermatitis	5

TABLE 4.—*Data About Controls*

No.	Name	Sex	Age, Yr.	Coloration		Status
				Hair	Eyes	
1	H. C.	M	28	Brown	Brown	Hospitalized for orthopedic disorder
2	D. V.	F	41	Gray	Brown	Hospitalized for psychiatric disorder
3	D. J.	M	35	.....	.....	Hospitalized for psychiatric disorder
4	M. Z.	M	26	Brown	Blue	Hospitalized for psychiatric disorder
5	W. S.	M	27	Brown	Blue	Hospitalized for psychiatric disorder
6	L. P.	M	23	Brown	Blue	Hospitalized for psychiatric disorder
7	L. N.	F	46	Gray	Blue	Hospitalized for psychiatric disorder
8	A. T.	M	32	Black	Brown	Hospitalized for psychiatric disorder
9	R. B.	M	37	Red	Blue	Hospitalized for psychiatric disorder
10	D. C.	F	40	Blond	Blue	Hospitalized for psychiatric disorder

seconds. The reactions were evaluated immediately and after an interval of five minutes.

Before we began the actual testing of the controls and patients of this study, an additional 47 subjects, consisting of physicians, nurses, secretaries, and unselected patients with a variety of cutaneous diseases, were tested so that the technique might be standardized as completely as possible.

The threshold of pain was determined by a device invented by George Mount, Ph.D., of the University of California at Los Angeles. The instrument is essentially a tiny, especially designed coil, heated electrically by a combination of currents which brings the temperature immediately to a predetermined level for a selected interval of time and then cools off at once. It is diagrammatically pictured in Figures 5 and 6. The threshold is expressed in units of an arbitrary scale.

MATERIAL

A total of 24 patients and controls was studied. Of the 14 patients 13 had the dry type of neurodermatitis and 1 pruritus ani. Pertinent data about the patients are given in Table 3. Ten subjects served as controls. Of these, nine were hospitalized patients with neuroses, and one had an orthopedic disorder. Relevant data are presented in Table 4.

TABLE 5.—*Salient Psychologic Characteristics of Patients* *

No.	Obsessive-Compulsive	Paranoid	Schizoid	Hysterical	Character Disorder	Impulse Neurosis	Hostile	Depressed	Exhibitionistic	Sexual Disturbances: Heterosexual	Sexual Disturbances: Homosexual	Adjustment
1	++	+	....	....	....	..	+	+	..	+	..	Precarious
2	....	..	....	....	++	+	+	+	..	+	..	Poor
3	++	..	....	....	....	..	+	+	..	+	..	Fair
4	++	..	....	....	....	..	+	+	..	+	..	Fair
5	++	..	....	....	....	..	+	+	..	+	..	Fair
6	....	..	....	++	....	..	..	..	+	..	..	Adequate
7	++	..	....	....	....	..	..	..	..	..	+	Adequate
8	....	..	++	....	....	..	..	..	..	..	+	Fair
9	++	..	....	....	....	..	+	..	..	..	+	Fair
10	++	+	+	....	....	..	+	..	+	..	+	Precarious
11	++	..	....	....	....	..	+	+	+	..	..	Adequate
12	....	+	++	+	....	..	+	+	+	..	..	Gravely impaired
13	....	..	....	....	++	+	+	..	+	..	..	Fair
14	++	..	....	....	....	..	+	+	..	+	..	Fair

* Major trend is indicated by ++; minor trend, by +.

TABLE 6.—*Salient Psychologic Characteristics of Controls* *

No.	Obsessive-Compulsive	Paranoid	Schizoid	Hysterical	Character Disorder	Impulse Neurotic	Hostile	Depressed	Acting-Out Tendency	Sexual Disturbances: Heterosexual	Sexual Disturbances: Homosexual	Adjustment
1	....	..	....	....	++	+	..	..	..	..	..	Good
2	++	..	....	....	....	..	+	..	..	..	+	Fair to poor
3	++	+	+	....	....	..	..	+	..	..	+	Precarious
4	++	..	....	....	....	..	..	+	..	..	..	Fair
5	....	+	++	+	....	..	..	..	..	..	..	Poor to fair
6	....	..	....	....	++	+	..	..	+	..	..	Poor to fair
7	++	..	+	....	....	..	..	..	..	..	..	Poor to fair
8	+	++	+	....	....	..	..	..	..	..	..	Poor to fair
9	....	..	....	....	++	+	+	..	+	..	..	Poor to fair
10	++	..	....	....	+	..	+	..	..	..	..	Poor to fair

* Major trend is indicated by ++; minor trend, by +.

The outstanding characteristics of the patients' personalities as determined by the projective tests are recorded in Table 5 and comparable data for the controls in Table 6. It should be noted that 4 of the 10 controls were selected because such factors as sex, age, and occupation were comparable to those of the patients. The other six, who had already been tested by the projective techniques used in this study, were chosen because their personalities matched so well those of six of our patients.

The determinations of the reactions to histamine and the pain thresholds for the patients and the controls are given in Tables 7 and 8, and those for the subjects of the preliminary tests in Tables 9 and 10.

TABLE 7.—*Reactions to Histamine and Pain Thresholds of Patients*

Patient No.	Reactions to Histamine,* Duration of Exposure, Sec. 5	10	15	20	25	30	Comment	Pain Threshold†
1	1+	1+	2+	2+	2+	3+	.....	580
2	1+	1+	1+	1+	1+	2+	Tested twice	560
3	—	1+	1+	2+	2+	2+	.....	580
4	±	1+	2+	3+	3+	3+	.....	Not tested
5	...	...	...	...	...	...	Not tested	520
6	1+	1+	2+	2+	2+	2+	Tested twice	540
7	1+	1+	2+	2+	2+	2+	.....	680
8	—	—	1+	1+	2+	2+	.....	640
9	2+	4+	4+	4+	4+	4+	.....	...
10	—	—	—	—	—	—	.....	...
11	2+	4+	4+	4+	4+	4+	.....	...
12	2+	3+	4+	4+	4+	4+	.....	...
13	—	—	1+	—	—	—	.....	540
14	4+	4+	...	...	...	...	Test discontinued because of severity of reaction	...

* Reactions were evaluated as follows: — no reaction; ± equivocal reaction; 1+ erythema; 2+ erythema and papules; 3+ erythema, papules, and edema; 4+ erythema, papules, edema, and peripheral whealing.
† Expressed in arbitrarily selected units.

TABLE 8.—*Reactions to Histamine and Pain Thresholds of Controls*

Control No.	Reactions to Histamine,* Duration of Exposure, Sec. 5	10	15	20	25	30	Pain Threshold†	Comment
1	±	—	—	1+	2+	2+	...	.....
2	—	—	±	1+	1+	2+	No pain	Dilated pupils
3	—	—	1+	1+	1+	2+	610	.....
4	—	—	—	1+	2+	3+	600	.....
5	—	—	—	—	—	—	No pain	Dilated pupils
6	—	1+	2+	3+	3+	3+	640	.....
7	1+	1+	1+	2+	3+	4+	500	Very painful
8	—	—	—	—	—	—	No pain	.....
9	—	—	1+	2+	3+	4+	510	.....
10	—	—	1+	1+	1+	1+	580	.....

* Reactions were evaluated as follows: — no reaction; ± equivocal reaction; 1+ erythema; 2+ erythema and papules; 3+ erythema, papules, and edema; 4+ erythema, papules, edema, and peripheral whealing.
† Expressed in arbitrarily selected units.

TABLE 9.—*Pain Thresholds of Sixteen Unselected Subjects of Preliminary Tests*

No.	Name	Sex	Age, Yr.	Coloration Hair	Coloration Eyes	Pain Threshold*
1.....	J. B.	M	25	.....	.....	610
2.....	M. O.	M	55	Brown	Blue	600
3.....	M.	M	30	Blond	Brown	540
4.....	R. B.	M	27	Brown	Brown	620
5.....	J. W.	M	49	Brown	Brown	560
6.....	J. T.	F	28	Brown	Brown	520
7.....	D. V.	F	25	Brown	Blue	540
8.....	E. G.	F	35	Blond	Green	620
9.....	K. D.	M	28	Blond	Blue	540
10.....	A. G.	M	27	Brown	Blue	620
11.....	R. B.	M	50	Red	Blue	620
12.....	J. W.	M	56	Brown	Blue	...
13.....	C. M.	M	33	Brown	Blue	...
14.....	F. C.	M	40	Brown	Brown	640
15.....	B. C.	M	31	Brown	Blue	600
16.....	H. C.	M	39	Blond	Blue	...

* Expressed in arbitrarily selected units.

TABLE 10.—*Reactions to Histamine of Forty-Seven Unselected Subjects of Preliminary Tests*

No.	Name	Sex	Age, Yr.	Coloration		Diagnosis	Reactions to Histamine,* Duration of Exposure, Sec.					
				Hair	Eyes		5	10	15	20	25	30
1	J. B.	M	25	.....	.....	.....	—	—	—	—	±	1+
2	M. O.	M	55	Brown	Blue	No disease	—	—	—	—	1+	1+
3†	M.	M	30	Blond	Brown	No disease	—	1+	1+	2+	3+	...
4	R. B.	M	27	Brown	Brown	No disease	—	—	1+	1+	2+	2+
5	J. W.	M	49	Brown	Brown	No disease	1+	1+	1+	2+	2+	1+
6	J. T.	F	28	Brown	Green	No disease	—	—	—	—	—	—
7	D. V.	F	25	Brown	Blue	No disease	—	—	—	—	—	—
8	E. G.	F	35	Blond	Green	No disease	—	—	—	1+	1+	1+
9	H. M.	F	40	Brown	Brown	No disease	±	1+	2+	3+	4+	4+
10	J. T.	M	31	Brown	Brown	Pruritus ani	—	1+	2+	2+	2+	2+
11	H. R.	F	34	Brown	Brown	Contact eczema	3+	3+	3+	3+	3+	3+
12	M. T.	F	34	Brown	Brown	Neurodermatitis	—	—	—	—	—	—
13	V. H.	F	33	Blond	Blue	Alopecia areata	1+	1+	1+	1+	1+	1+
14	J. M.	M	31	Brown	Blue	Neurodermatitis	—	—	—	—	—	—
15	M. A.	M	26	Black	Brown	Psoriasis	—	—	—	—	—	—
16	C. H.	M	60	Bald	Blue	Psoriasis	1+	2+	2+	3+	3+	1+
17	C. M.	M	33	Brown	Blue	Central nervous system syphilis	—	1+	1+	2+	3+	3+
18	F. C.	M	40	Brown	Brown	Osteomyelitis	2+	2+	2+	2+	2+	2+
19	B. C.	M	31	Brown	Blue	Osteomyelitis	2+	2+	2+	3+	4+	...
20	H. C.	M	39	Blond	Blue	Osteomyelitis	—	—	1+	1+	2+	2+
21	R. B.	M	50	Red	Blue	Neurodermatitis	3+	3+	3+	4+	4+	...
22	J. W.	M	56	Brown	Blue	Neurodermatitis	—	1+	1+	2+	2+	2+
23‡	H. L.	M	36	Brown	Hazel	No disease	—	—	1+	...	...	...
24	V. W.	F	27	Blond	Blue	No disease	—	—	1+	...	...	...
25	W. P.	M	37	Brown	Blue	No disease	—	—	—	1+	...	...
26	B. L.	F	24	Brown	Hazel	No disease	—	—	1+	...	...	...
27	L. R.	M	36	Brown	Brown	No disease	—	—	1+	...	...	...
28	R. S.	M	39	Brown	Hazel	No disease	—	—	1+	...	...	...
29	M. B.	F	21	Red	Blue	Neurodermatitis	—	1+	...	...	...	...
30	J. F.	M	29	Brown	Brown	Neurodermatitis	—	—	1+	...	...	...
31	R. C.	M	13	Brown	Brown	Neurodermatitis	—	—	1+	...	...	...
32	A. M.	M	59	Brown	Brown	Neurodermatitis	—	—	1+	...	...	...
33	Z.	M	42	Brown	Brown	Neurodermatitis	—	—	1+	...	...	...
34	N.	F	4	Blond	Brown	Neurodermatitis	—	1+	...	...	...	...
35	L. L.	M	28	Brown	Brown	Lichen simplex chronicus	—	—	1+	...	...	...
36	S.	F	29	Brown	Hazel	Contact eczema	—	—	1+	...	...	...
37	M. S.	F	29	Brown	Blue	Acne vulgaris	—	—	1+	...	...	...
38	A.	M	52	Brown	Hazel	Psoriasis	—	1+	...	...	...	...
39	R. S.	F	61	Brown	Brown	Pruritus ani	—	1+	...	...	...	...
40	M. S.	M	49	Brown	Brown	Pruritus ani	—	—	—	1+	...	...
41	A. B.	F	56	Brown	Brown	Pruritus ani	—	—	1+	...	...	...
42	S. T.	M	67	Brown	Brown	Pruritus ani	—	—	1+	...	...	...
43	S. T.	F	28	Blond	Blue	Urticaria	1+	...	...	...	...	...
44	N. C.	F	22	Black	Brown	Urticaria	1+	...	...	...	...	...
45	J. K.	M	40	Brown	Blue	Urticaria	1+	...	...	...	...	...
46	W. F.	M	28	Blond	Blue	Urticaria	1+	...	...	...	...	...
47	T.	F	31	Brown	Hazel	Urticaria	—	1+	...	...	...	...

* Reactions were evaluated as follows: — no reaction; ± equivocal reaction; 1+ erythema; 2+ erythema and papules; 3+ erythema, papules, and edema; 4+ erythema, papules, edema, and peripheral whealing.

† Test discontinued because of severity of reaction.

‡ Exposure discontinued with appearance of erythema in Patients 23 to 47.

RESULTS

Although compulsive-obsessive characteristics were present in a preponderance of the patients and hysterical trends were evident in a fair number, no consistent psychologic structure, common to all, emerged. Some patients, in fact, displayed neither compulsive nor hysterical tendencies. The absence of a common pattern is not surprising, because six of the controls, who had no cutaneous disease, displayed qualities of personality quite comparable to those of the patients. It appears, then, that subjects with neurodermatitis show neurotic trends which are in no way specific for the cutaneous disease.

Among the more detailed characteristics which were disclosed in many of the patients was a pronounced tendency to turn hostile or aggressive impulses inward, against themselves, rather than against the external target which a normal person would choose. The propensity to bottle up emotions was much more common than in neurotic personalities in general. One can only wonder whether such bottling up of emotions and impulses creates a need for peculiar outlets. Is it possible that some cutaneous diseases are an expression of accumulated tension?

It is of interest that in many instances the Rorschach test disclosed a strong concern with tactile sensations and touch, because we have frequently observed clinically that patients with neurodermatitis are preoccupied with ideas of contact, often evincing a morbid disinclination to be touched by others while gaining great satisfaction from the scratching of their own skins. The patients' awareness of the skin, disclosed by the Rorschach test, was also evident in the results of the draw-a-person tests. Their preoccupation with their reactive outer covering was evinced on the one hand by the hesitancy, even delicacy, with which they traced the outline, that is, the skin, of the human figures and on the other by the loving care displayed in the shading and details of the drawings. Such interests were much less common in the controls' sketches.

Since the results, though far from conclusive, seem to indicate that further investigations might produce data of significance, more patients are being studied, and the psychologists who collaborated in this project will report at a later date the detailed observations on the entire series.

It became immediately apparent that no normal range of reactivity to histamine could be established. Of the group of 47 unselected subjects, tested while the technique was being mastered, some were nonreactors while others showed reactivity ranging from equivocal, or minimal, to strongly positive. The results for the patients with unselected cutaneous diseases were equally contradictory. There was no homogeneity of response even among patients with the same cutaneous disease. For example, one patient with psoriasis showed a definite reaction, and another, none at all. The single exceptions were the patients with urticaria, all of whom reacted within five seconds. Likewise, the reactions of the patients of this study were equally inconclusive because they ranged all the way from negative to pronounced.

Study of all the tabulated data disclosed one unexpected fact, namely, that many of the subjects who reacted weakly or not at all were fair-skinned and blue-eyed, while hyperreactors often had dark skins and brown eyes. While not of statistical significance, this observation is of considerable interest.

We are well aware of the host of variables which may have contributed to the inconstant results. For example, variations in temperature, electric current, and the patient's state of mind could have had a strong bearing on the reactions.

There was no discernible difference between the pain thresholds of the patients, the controls, and the unselected subjects tested in the preliminary stages of the study. No consistent relation between the pain threshold and the degree of reactivity to histamine emerged. The instrument is new and has not had sufficiently widespread application to make possible the accumulation of comparable data by other workers. We hope to use it on a much larger series of patients.

SUMMARY

Fourteen patients, thirteen with the dry type of neurodermatitis and one with pruritus ani, and ten controls were studied by projective tests. No psychologic structure common to all the patients emerged, an outcome at variance with the published results of most psychiatric studies. The personality of the patient with neurodermatitis is in no way specific for his cutaneous disease.

No ranges of pain thresholds or reactions to histamine were established for either controls or patients, and no consistent relation between the responses to the two types of cutaneous stimuli was discernible.

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ABSTRACT OF DISCUSSION

Dr. Frank E. Cormia, New York: Dr. Obermayer and his associates are to be congratulated for their attempts to apply objective techniques in patients with functional dermatoses. The utilization of psychometric tests in these diseases is a relatively new approach, and I hope they will extend it to include patients with other psychosomatic skin disorders. There is, however, a considerable difference of opinion regarding the relative interpretive value of the projective tests. As a rule, psychiatrists utilize them to confirm knowledge obtained by clinical analytic methods; for this, and particularly for research studies, such tests as the Rorschach are of great value. However, they only rarely uncover material not obtained by adequate clinical methods. Furthermore, these tests, notably the Rorschach, tend to focus attention on abnormalities rather than on normal functions. In consequence, false impressions may be created and minor psychopathologic trends exaggerated and distorted. These pitfalls can be avoided only by combining the tests with a thorough clinical evaluation.

Many psychiatrists do not believe that the results of projective tests are superior to those obtained by a complete clinical examination and history. All of a group recently questioned felt that the reverse was true. For the actual management of patients, detailed knowledge of the life situation is of fundamental importance. Dr. Obermayer utilized the Otis intelligence test to complete his data; he recognizes, of course, the variations which may be encountered depending on the selection of material.

Specifically, in personal studies on patients with atopic dermatitis in hospital, as contrasted with office patients, not only was there wide divergence in intelligence levels but also in personality structure in relation to width of interests, imagination, aggressiveness, compulsive tendencies, etc.

Dr. Obermayer concluded that patients with neurodermatitis display varied neurotic trends and personality structure not specific for their cutaneous disease. This observation coincides with my findings, not only in atopic dermatitis but also in the various other categories of psychosomatic cutaneous disease. However, 9 of his 14 patients showed obsessive-compulsive features with predominantly hostile emotional reactions. This finding was noted in my material. I would recommend that a larger series be studied, and the significance of these findings be determined by clinical evaluation. Such features as compulsion, overawareness, and preoccupation with one's skin should be studied in patients with neurodermatitis of both short and pro-

longed duration. That, is how many of these traits are primary, and how many are subsequential in nature? In further studies it might be worth while also to select controls at random from patients with nonpsychosomatic skin disorders, since but little differences would be expected in patients with atopic dermatitis and those with neuroses.

Dr. Obermayer has undertaken a fascinating study with his investigation of cutaneous reactivity to histamine and estimation of pain thresholds in patients with psychosomatic dermatoses. During the past year I have been studying the effect of histamine on such patients. My interests, however, have centered on the production of itching rather than the objective cutaneous reaction to histamine. Fortunately, I have been able to utilize the large experience of Dr. Walter Shelley on the cutaneous effects of histamine. In his studies on pruritus he demonstrated both qualitative and quantitative variability of results as produced by Mucuna pruriens (itch powder) and histamine by iontophoresis. He considered both to be unreliable for the production of a standardized itch response. With regard to histamine he showed further that standard solutions varied greatly in their physiologic activity; some were inert. This fact may explain the absence of cutaneous response in some of Dr. Obermayer's patients. Histamine solutions should be freshly prepared.

Following Dr. Shelley's suggestion I was able to obtain rather constant physiologic responses when utilizing a quantitative intradermal technique. A general correlation between the intensity of the histamine reaction and the severity of associated pruritus was present. Moreover, a demonstrable increase in the size of the histamine reaction and a definite lowering of the itch threshold could be obtained following psychic stress. There may be further objections to an iontophoretic technique. Cutaneous absorption of histamine may vary not only with the intensity of current but also with variations in temperature, blood supply, amount of surface sebum, number of follicular openings and their state of patency, and the electrical resistance of the skin. The latter property of the skin has been shown by Furer and Hardy and by others to vary greatly depending on the patient's reaction to stress and on his adaptation to stress situations.

Hardy and his associates believe that pain thresholds as determined by the Hardy-Wolff-Goodell pain threshold apparatus are relatively constant under uniform physical conditions. The reaction to pain, pain sensitivity, on the contrary, depends to a certain extent on the functional state of the nerve pathways between the skin and the sensory cortex. Rothman, Graham, I, and others believe that itching is a modified form of pain transmitted on pain fibers. However, variations in the type and intensity of the applied stimulus and in the physical and functional state of the diseased skin result in an evident lack of correlation between itching and pain thresholds, as found by Potelunas, Meixner, and Hardy. Thickened skin usually has a high pain threshold, yet, I found the itch threshold to be extremely low. Both pain and itch thresholds may be lowered in areas of active dermatitis, regardless of the cause. There is no question in my mind that the itch threshold, calibrating as it does fine differences of cutaneous irritability, is a more sensitive measuring stick than is the pain threshold in the study of functional disorders of the skin.

Dr. Martin F. Engman Jr., St. Louis: We have been interested for many years in disseminated neurodermatitis and have published some work on the disease. The question of cause is always in mind. The neurogenic theories are popular, and there is some evidence to support them. However, the proneurogenic arguments often seem to us to have the cart before the horse.

Dr. Obermayer has done a splendid and impressive piece of work. Interpretation of his evidence, however, may be made in another direction. Think of a person who has a constant handicap. It does not debilitate him but may be sufficiently annoying to made certain changes in his personality.

It seems to me that the object of the experiment should be a study of the affect of the disease on the personality rather than simply a study of certain departures from normal or average present in persons suffering from the disease. These tests should be repeated when the condition has been in remission for a considerable period of time. Also, parallel studies should be made in cases of chronic diseases which could have a similar affect on the personality, such as mild types of chronic arthritis in which there is recurrent and chronic pain. Such studies would serve as controls.

DR. THOMAS H. STERNBERG, Los Angeles: For the 32 patients with atopic dermatitis upon whom I reported at this meeting we did Rorschach and thematic apperception tests. We also studied similarly two groups of controls. The first was persons with other chronic skin diseases who were under similar circumstances, namely, hospitalized. In the second group the controls were similar to Dr. Obermayer's; that is, we used anyone we could find who was apparently normal. I say "apparently" because I understand that some of our psychiatrists contend that no one is in this category.

Our results were in complete agreement with those reported by Dr. Obermayer. In the first place, it is true that persons with atopic dermatis did have a large incidence of compulsive-obsessive tendencies. They tended to be hostile. They had insecure feelings and so forth. When the results of the tests were compared against the two control groups, however, it was found that there was no significant difference among the three groups, and no significant pattern could be established.

It is of some interest that the great majority of our "normal" control group were graduate students working toward their Ph.D. degrees, and I assume that they would be compulsive anyway. An additional finding in the test group was that the Piatrowski check list of the Rorschach test revealed no evidence of organic brain disease.

DR. MAXIMILLIAN E. OBERMAYER, Los Angeles: As I mentioned before, this is the report on a pilot study which may branch out in many different directions. Dr. Engman's suggestion is certainly constructive and worth following. I was most gratified to hear Dr. Sternberg's comments. In this connection I should like to say that one of the psychologists who cooperated in this study showed the results of the tests to an unbiased expert on projective techniques who has had no contacts with our patients. That expert unerringly separated the patients from the controls.

As to Dr. Cormia's remarks, I cannot see why the projective techniques should be less reliable than clinical psychiatric investigation. Granted that the findings obtained by psychoanalysis or from thorough study by a competent psychiatrist are likely to be more accurate, the results of projective techniques are certainly far more dependable than the information which the dermatologist is able to elicit. Of course there is a subjective element in their interpretation, but I know of no technique which is free from it. I was interested in Dr. Cormia's statement that he also had trouble with the histamine test with iontophoresis. We shall try to change the technique, or, if this should not be profitable, substitute other tests.

I should like to make it perfectly clear that I do not believe that the emotional and psychic structure of the patient is the cause of neurodermatitis. It is merely a concomitant part of the often hereditary syndrome which includes allergic reactions and a propensity to vascular disturbances, but I do believe that the piling up of neurotic tensions is the most important factor in the causation of acute exacerbations.

There is one more point I should like to make: In my opinion the attempts to pigeonhole the various neurotic trends in patients with neurodermatitis and to classify them as obsessive and hysterical have been hopeless. I believe that this study has shown that a search for highly specific attitudes and trends would be a more promising approach. For instance, the bottling up of emotions instead of acting them out is a trait common to a large group of neurotic persons, but the bottling up of certain specific emotions, such as conflicts about contact in both the actual and the symbolic sense, may possibly be characteristic of persons who have a certain cutaneous disease.

HIDRADENITIS AND OTHER VARIANTS OF ACNE

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HIDRADENITIS suppurativa and the more severe types of acne, such as acne conglobata and dissecting cellulitis of the neck and scalp, not infrequently occur in the same persons. These disorders have been described as distinct entities; however, in clinical characteristics and in the course of the disease, they have many similarities which indicate a close relationship among them. They may be considered as regional counterparts in which the acne process is manifested in its extreme variants and in its more fulminating forms. Acne conglobata, dissecting cellulitis, hidradenitis, and other variants of acne have these features in common: functional glandular hyperplasia of the apocrine gland and pilosebaceous apparatus; double comedo formation and impaction of the follicular orifice; bacterial invasion with suppuration and undermining of the loose areolar tissue, and eventual healing with cicatrization and not infrequent keloid formation.

This presentation is concerned with a correlation of various aspects of the clinical features, with the pathologic physiology and anatomy, the functional relationship between the apocrine gland and the pilosebaceous apparatus, and with an appraisal of the genetic, hormonal, and infectious components.

REVIEW OF THE LITERATURE

The literature on hidradenitis, acne conglobata and dissecting cellulitis is not extensive. Hidradenitis suppurativa was originally described by Velpeau [1] in 1839 as an entity, on the basis of the peculiar distribution of the disease, involving selected sites of the cutaneous surface, such as the axillary, mammary, inguinal, genital, and perianal regions. Verneuil,[2] a French surgeon, in 1854 first observed the association of the disease with abscesses of the sweat glands; however, it was not until 1922, when Schiefferdecker [3] described the apocrine type of sweat gland, that the biologic significance of this modified type of sweat gland was recognized in relation to this

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1. Velpeau, cited by Verneuil, A.: Arch. gen. méd. **94**:447 and 693, 1854; ibid. **114**:537, 1864; ibid. **115**:327 and 437, 1865.

2. Verneuil, A.: Études sur les tumeurs de la peau: de quelques maladies des glandes sudoripares, Arch. gen. méd. **94**:447 and 693, 1854; De l'hidrosadenite phlegmoneuse et des abces sudoripares, ibid. **114**:537, 1864; **115**:327 and 437, 1865.

3. Schiefferdecker, P.: Über morphologische Sekretionserscheinungen in den ekkrinen Hautdrüsen des Menschen, Arch. Dermat. u. Syph. **132**:130, 1921; Die Hautdrüsen des Menschen und der Saugetiere, ihre biologische und rassenanatomische Bedeutung, sowie die Muscularis sexualis, Stuttgart, E. Scheizerbert, 1922.

peculiarly regionally distributed disease. Pollitzer [4] (1892) and Dubreuilh [5] (1893), under somewhat similar titles, described what they believed to be abscesses of the sweat glands; however, these were later recognized as papulonecrotic tuberculids. Subsequent articles on hidradenitis include those of Lane [6] (1933) and Brunsting [7] (1939).

Acne conglobata was originally described by Spitzer [8] (1901) and later by Lang [9] (1902) and Reitman [10] (1908). More extensive descriptions with histologic studies include those of Michelson and Allen [11] (1931) and Belote [12] (1933).

Dissecting cellulitis of the scalp has been described by Spitzer [13] (1903) and Nobl [14] (1905). Hoffman [15] (1908) designated the disease as "perifolliculitis capitis abscedens et suffodiens." Wise and Parkhurst [16] (1921) discussed the disorder as "a rare form of suppurating and cicatrizing disease of the scalp." Barney [17] (1931) reviewed the literature, discussed the clinical and histologic features, and, following the suggestion of Pusey, designated the disease as "dissecting cellulitis of the scalp."

The presence in the same person of hidradenitis and either acne conglobata or dissecting cellulitis of the scalp has been the subject of case reports at various dermatologic meetings.[18] Goeckerman,[18g] in discussing this interesting phenomenon,

4. Pollitzer, S.: Hydradenitis Destruens Suppurativa, J. Cutan. Dis. **10**:9, 1892.

5. Dubreuilh, W.: Des hidrosadenites suppuratives disseminées, Arch. méd. exper. et anat. path. **5**:63, 1893.

6. Lane, J. E.: Hidrosadenitis Axillaris of Verneuil, Arch. Dermat. & Syph. **28**:609, 1933.

7. Brunsting, H. A.: Hidradenitis Suppurativa; Abscess of the Apocrine Sweat Glands, Arch. Dermat. & Syph. **39**:108 (Jan.) 1939.

8. Spitzer, L.: Dermatitis Follicularis et Perifollicularis Conglobata, Dermat. Ztschr. **10**:8, 1901.

9. Lang, E.: Hautkrankheiten, Wiesbaden, J. F. Bergmann, 1902, p. 504.

10. Reitman, K.: Acne Aggregata seu Conglobata, Arch. Dermat. u. Syph. **90**:249, 1908.

11. Michelson, H. E., and Allen, P. K.: Acne Conglobata, Arch. Dermat. & Syph. **23**:49 (Jan.) 1931.

12. Belote, G. H.: Acne Conglobata: An Experimental Study, Arch. Dermat. & Syph. **27**:302 (Feb.) 1933.

13. Spitzer, L.: Dermatitis follicularis et Perifolliculitis conglobata, Dermat. Ztschr. **10**:109, 1903.

14. Nobl, G.: Follicularprocess der Kopfhaut mit Harrausfall, Arch. Dermat. u. Syph. **74**:80, 1905.

15. Hoffman, E.: Zwei Patienten mit narbiger Alopecie, Dermat. Ztschr. **15**:122, 1908.

16. Wise, F., and Parkhurst, H. J.: A Rare Form of Suppurating and Cicatrizing Disease of the Scalp, Arch. Dermat. & Syph. **4**:750 (Dec.) 1921.

17. Barney, R. E.: Dissecting Cellulitis of the Scalp, Arch. Dermat. & Syph. **23**:503 (March) 1931.

18. (*a*) Hauck, L.: Beitrag zur Ätiologie der Folliculitis et Perifolliculitis suffodiens et abscedens (E. Hoffman), Dermat. Ztschr. **53**:275, 1928. (*b*) Veiel, F.: Perifolliculitis abscedens et suffodiens und ihre Beziehung zur Acne conglobata, ibid. **53**:674, 1928. (*c*) Cueni, S.: Zur Kenntnis der Pathogenese der Perifolliculitis capitis abscedens et suffodiens (E. Hoffman) und ihrer Beziehungen zur Acne conglobata, ibid. **51**:94, 1928. (*d*) Highman, W. J., in discussion on Eller, J. J.: Perifolliculitis Capitis Abscedens et Suffodiens, Arch. Dermat. & Syph. **17**:272 (Feb.) 1928. (*e*) Shaffer, L. W.: Perifolliculitis Capitis Abscedens et Suffodiens, ibid. **21**:139 (Jan.) 1930. (*f*) O'Leary, P. A.; Montgomery, H., and Brunsting, L. A.: Acne Conglobata, Pyoderma, and Hidradenitis Suppurativa, ibid. **47**:725 (May) 1943. (*g*) Goeckerman, W. J., in discussion on Anderson, N. P.: A Case of Perifolliculitis Capitis Abscedens et Suffodiens, Cutis Vertices Gyrata, Hidradenitis Suppurativa, ibid. **42**:492 (Sept.) 1940.

stated that he has long felt that there was a close etiologic relationship among these diseases.

SEX INCIDENCE

The distribution of acne vulgaris between the sexes is about equal, the disease probably being slightly more common in males. Bloch,[19] in an extensive survey of 4,191 children between the ages of 6 and 19 years, reported the occurrence of acne or numerous comedones in 59% of the girls and in 68% of the boys. He stated that, on the whole, acne vulgaris occurred in every 7th child, and that it was present in every 5th boy and in every 12th girl in this age group. The more severe types of acne, such as acne conglobata which is characteristic of the postadolescent period, are extremely rare in women. The occurrence of dissecting cellulitis of the scalp and neck is almost exclusively limited to males, usually between the ages of 20 and 40.

In my experience, following a report of 22 cases [7] and subsequent observation in 17 others, hidradenitis is approximately equally common between the sexes. When the disease involves only the axillary region, it is more common in females. This cannot be explained alone on the basis that the use of deodorants and depilatories and shaving of the axillary hair are more common practices among women and girls. I consider such superficial irritation and infection of the skin of secondary importance rather than a predisposing causative factor.

CLINICAL AND HISTOLOGIC CHARACTERISTICS

The clinical features of acne conglobata, dissecting cellulitis, and hidradenitis have much in common, and are well known. Considerable space in the literature has been devoted to a detailed description of each of these disorders [20]; however, in their objective characteristics, they have so much in common that a brief clinical description of one disorder well fits the other. Depending on the stage of the disease, and on the degree of involvement, these disorders are characterized by double comedo formation, the presence of abscesses, communicating channels, discharging sinuses, and eventual healing with residual keloidal or so-called bridge scars. The anatomic nature of the loose areolar tissue present in the scalp, axillary, mammary, and anogenital regions lends facility to the frequent burrowing characteristic of these diseases.

The presence of multiple comedones is common in all three disorders. Comedo, from the Latin, *comedere,* to eat up, literally means a glutton. When a comedo is expressed from the skin, it has a worm-like appearance, and it was formerly believed that there was an actual worm present which ate into the flesh. In acne conglobata, as Michelson and Allen [11] emphasized, the comedones are often the forerunners of the inflammatory process, are exceptionally large, and occur in groups of 10 to 20 or more. Barney,[17] in discussing dissecting cellulitis of the scalp, remarked that whereas comedone formation is not as striking and as constant a feature as in acne conglobata, nevertheless, it does occur. In hidradenitis, the presence of dilated follicular orifices and double comedones of the axillary, genital, perianal, and mammary regions is a common, frequently overlooked, and underestimated feature.

19. Bloch, B.: Metabolism, Endocrine Glands and Skin Diseases, with Special Reference to Acne Vulgaris and Xanthoma, Brit. J. Dermat. **43**:61 (Feb.) 1931.

20. Brunsting.[7] Michelson and Allen.[11] Barney.[17]

According to Montgomery,[21] the double comedo is believed to arise from the merging of two or more glands in close proximity by pressure atrophy of the tissues which ordinarily separate them, thus forming one cavity with two or more ducts. The first phase in the acne process is the formation of the comedo. In the early stage the histologic process is characterized by a superficial hyperkeratosis of the epidermis, which, extending to the mouth of the follicular orifice, leads to the formation of the comedo. What factor induces the hyperkeratosis about the neck of the follicle remains obscure. It is believed by some to be the result of irritation produced by organisms; however, it appears that this feature is of secondary rather than primary significance. Lynch,[22] in a review of the histologic changes observed from early lesions of 30 patients with acne, found no clues to explain the nature of the mechanism of production of the comedo. He concluded that

> the inflammatory phase of the acne papule can arise without apparent rupture of the follicle and without demonstrable bacterial invasion of the follicle wall, the glands or the connective tissue. The papule frequently develops as an inflammatory reaction around remnants of atrophic sebaceous glands which are perhaps a sequel to the stasis and pressure caused by the comedo within the follicle.

Sutton Jr.[23] has stated that the acne process may be a result of improper balance between the intake of lipoids and their proper metabolism and that histologically it is a foreign-body reaction to lipoid. Montgomery [21] has expressed the opinion that the histologic evidence is against acne being associated with lipoidosis. Michelson and Allen [11] concluded that the histopathologic features of acne conglobata in the main resembled those of acne vulgaris. The changes observed varied with the age of the lesion, but certain features were found in almost all stages of the disease. Histologically, they were in accord with other observers and concluded that the process is closely allied to the severe types of acne vulgaris.

In hidradenitis, as in the acne process, the histologic characteristics in the early stage consist of a folliculitis which is followed by a severe perifolliculitis and extension of the process in the deep layers of the skin involving the apocrine gland. Barney [17] stated that the actual relationship of dissecting cellulitis and acne conglobata could not be determined. However, one can conclude that in the age of onset, sex distribution, and clinical and histologic features a great similarity exists.

ANATOMIC AND FUNCTIONAL RELATIONSHIP BETWEEN APROCRINE AND SEBACEOUS GLANDS

The aprocrine and sebaceous glands are similar in origin, in mode of function and secretion, and in anatomic relationship to the hair follicle. Both types of glands are derived from the hair follicle (anlage); the sebaceous gland develops during fetal life and becomes active soon after birth, whereas the apocrine gland does not function until puberty at the time of maturity of the sex glands. Functional hyperplasia of both glands occurs during adolescence. The apocrine and sebaceous glands function similarly by a rupture of the cell membrane with resulting evacuation of the cellular protoplasm into ducts which open directly into the hair follicle or on

21. Montgomery, H., in Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943, p. 1224.

22. Lynch, F. W.: Acne Vulgaris: Review of Histological Changes Observed in Early Lesions, Arch. Dermat. & Syph. **42**:593 (Oct.) 1940.

23. Sutton, R. L., Jr.: Acne Vulgaris: A Pustular Lipoidosis, South. M. J. **34**:1071, 1941.

the epidermis adjacent to the follicle, a process known as holocrine. Both types of glands are distributed over the surface of the skin only where hair exists. According to Way and Memmesheimer,[24]

> Vohwinkel examined material from many parts of the bodies of twenty Europeans and a larger number of Negroes from San Domingo. In one European only did he discover apocrine glands in a part of the body where they were not described by Schiefferdecker, namely, on the hypogastrium of a middle-aged man. One Negro had them on the forehead and the cheeks.
>
> If, as has already been stated, apocrine glands can occur only on those parts of the body where hair exists or has been, it is reasonable to believe that these glands can occur in uncommon areas in certain persons.

It has been stated that the apocrine glands occur twice as frequently and are better developed in women than in men; however, Way and Memmesheimer [24] concluded that they "occurred with the same frequency and seemed equally well developed in male and female subjects."

Cornbleet [25] recently observed the effect of pregnancy in two patients with hidradenitis suppurativa and one with Fox-Fordyce disease. In two patients the disease was very much improved during the pregnant state, only to relapse following delivery. The third patient was not followed after she came to term. He observed, after histologic study, that the apocrine glands are found more often in a resting state and secrete less during pregnancy than when the subject is in the nongravid state. From this he concluded that decreased functional activity during pregnancy may explain amelioration of apocrine gland diseases during gestation.

GENETIC FACTOR

It is probable that a genetic factor plays an important role in the origin of acne. In discussing inherited abnormalities of the skin, Cockayne [26] stated,

> Seborrhea and acne may depend upon two main factors, one external and the other genetic, though other factors of both kinds may also play a part. The chief external factor is infection with the specific organisms, which are ubiquitous, and the genetic factor is one that determines the development of large and active sebaceous glands. It is probably a simple dominant.

This statement is undoubtedly in error, for in the history of patients with acne, if both parents are free from the affection in as few as 10% of the cases, it is impossible for the condition to be inherited as a dominant trait, although dominant inheritance with incomplete penetration is not ruled out.

Stokes and King [27] stated that the incidence of acne in the parents of patients with acne is 26 times that in the parents of persons who have never had acne. Their statement that, "the heritable factors are probably complex and do not follow a simple mendelian distribution," although possibly correct, is not based on their published data. They present little or no evidence to support their conclusion, and in no way do they offer evidence as to what the genetic factor or factors may be.

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24. Way, S. C., and Memmesheimer, A.: The Sudoriparous Glands: II. The Apocrine Glands, Arch. Dermat. & Syph. **38**:373 (Sept.) 1938.

25. Cornbleet, T.: Pregnancy and Apocrine Gland Diseases: Hidradenitis, Fox-Fordyce Disease, A. M. A. Arch. Dermat. & Syph. **65**:12 (Jan.) 1952.

26. Cockayne, E. A.: Inherited Abnormalities of the Skin and Its Appendages, London, Oxford University Press, 1933, p. 351.

27. Stokes, J. H., and King, A. D.: Acne Vulgaris: Heredity in the Etiologic Background, Arch. Dermat. & Syph. **26**:456 (Sept.) 1932.

The studies of Siemens [28] offer satisfactory evidence in support of a genetic factor in the origin of acne. Identical twins with acne, selected because one twin had the disease, showed striking concordance in the degree of affliction in the members of each pair, while fraternal twins, selected on the same basis, showed marked discordance. Steinberg [29] has observed that almost twice as many of the patients' siblings have acne when one parent is affected as when neither parent is affected. On the basis of his unpublished material, he concludes that a genetic component is involved in the origin of acne and that further data of a more detailed nature are necessary before the nature of inheritance can be established.

HORMONAL FACTORS

The influence of the sex hormones, during adolescence, pregnancy, and the climacteric, upon the apocrine gland and the pilosebaceous apparatus is generally appreciated, but very little is known concerning the exact mechanism of their action. There is general agreement that an excess of androgens stimulates the surface epithelium and the sebaceous glands, tending to produce a seborrheic state with hyperkeratinization and resulting impaction of the hair follicle. Estrogenic stimulation has the opposite effect in inhibiting keratinization and the activity of the sebaceous glands.

It is well known that acne does not develop in eunuchs and eunuchoids. The influence of androgenic stimulation on the activity of the pilosebaceous apparatus has been conclusively shown by the experimental studies of Hamilton.[30] He treated nine eunuchoids and castrates with injections of testosterone propionate and observed the development of severe acne in seven. In an analysis of Hamilton's observations, Barber [31] stated,

> that as regards the effect on the pilo-sebaceous follicles, treatment of cryptorchids, eunuchs, and castrates with testosterone creates an artificial puberty, and the same march of events is noted: first, the awakening of sebaceous activity, which begins as at puberty on the central parts of the face; secondly, the formation of comedones at the ostia of some of the follicles; thirdly, in some cases the appearance of acne papules and pustules. Furthermore in the castrate, who had had acne severely in youth, under the influence of testosterone, a more intense eruption developed than in others who had not so suffered, thus illustrating the individual differences in the susceptibility of the follicles to hormonal influence that Bloch postulated, when he referred to variations in the "receptor mechanism."

Complete absence of androgenic stimulation is extremely rare, but when it occurs in such conditions as pituitary dwarfism and hypopituitary cachexia, the seborrheic state does not develop. In females, 17-ketosteroid excretion is an index of adrenal cortical function.[32] It rises at puberty, indicating increased adrenal activity that

28. Siemens, H. W.: Hereditary Pathology of Acne, München. med. Wchnschr. **73**:1514, 1926.

29. Steinberg, A. G.: Personal communication to the author.

30. Hamilton, J. B.: Acne—Male Hormone Substance: A Prime Factor in Acne, J. Clin. Endocrinol. **1**:570, 1941.

31. Barber, H. W.: The Influence of the Sex Hormones on the Skin and Pilosebaceous System, in Modern Trends in Dermatology, edited by R. M. B. MacKenna, London, Paul B. Hoeber, Inc., 1948, Chap. 6, p. 126.

32. Fraser, R.; Forbes, A. P.; Sulkowitch, H. W., and Reifenstein, E. C.: Colorimetric Assay of 17-Ketosteroids in Urine: Survey of Use of This Test in Endocrine Investigation, Diagnosis, and Therapy, J. Clin. Endocrinol. **1**:234, 1941.

accompanies that of the ovaries in the development of the secondary sex characteristics. It is generally appreciated that a disturbance of the androgen-estrogen ratio is of greater significance than an alteration in the estimated level of one or the other alone. This has been demonstrated in the studies of Wile, Snow, and Bradbury,[33] and by Lawrence and Werthessen.[34]

Sulzberger[35] stated that in one of his patients who was receiving androgen therapy for eunuchoidism a flare of hidradenitis of the axillae developed with each treatment. He also remarked that one can see the same effect of androgen in other glands of the skin, namely, in the related sebaceous glands and in the production of lesions of acne. Curtis[36] reported a case in which a 48-year-old woman had hidradenitis suppurativa of the axillae, breasts, and groin that was associated with typical signs of pituitary basophilism. In discussing this interesting and unusual phenomenon, he was of the opinion that its occurrence in the same patient was more than coincidental and reflected an increased androgenic stimulation.

The use of sex hormones in the treatment of acne has received considerable impetus in the past decade following the favorable reports of several investigators.[37] Some of these are presented with enthusiasm; however, in many, the number of patients observed is small, and rarely is there a proper control series, or follow-up study of relapse rate. The strongest supposition in favor of a hormonal factor in the evolution of acne is its appearance at puberty and its variation with the menstrual cycle, and there is controversy concerning the latter.

Development of the more severe forms of acne is characteristic of the postadolescent period. The majority of patients with these disorders are in the third or fourth decade, and have passed through the age of the usual simple acne process; however, all of them still exhibit the skin characteristic of the seborrheic state.

The term "tropical acne"[38] was coined during the last war to describe a variant of acne developing in military personnel stationed in the Pacific theater. The

33. Wile, U. J.; Snow, J. S., and Bradbury, J. T.: Studies of Sex Hormones in Acne: Urinary Excretion of Androgenic and Estrogenic Substances, Arch. Dermat. & Syph. **39**:200 (Feb.) 1939.

34. Lawrence, C. H., and Werthessen, N. T.: The Endocrine Dyscrasia of Acne Vulgaris in Women, Endocrinology **27**:755, 1940.

35. Sulzberger, M. B., in discussion on Ludy, J. P., and Drant, P.: Hidradenitis Suppurativa, Papulonecrotic Tuberculid and Bromoderma, Arch. Dermat. & Syph. **44**:494 (Sept.) 1941.

36. Curtis, A. C., in discussion on Wile, U. J., and Curtis, A. C.: Cushing's Syndrome with Hidradenitis Suppurativa, Arch. Dermat. & Syph. **58**:746, (Dec.) 1948.

37. Barber.[31] Lawrence, C. H., and Westhessen, M. J.: Treatment of Acne with Orally Administered Estrogens, J. Clin. Endocrinol. **2**:636, 1942. Cornbleet, T., and Barnes, B.: The Hormones and Acne Vulgaris: Urinary Assay for Therapeutic Use of Androgen, Arch. Dermat. & Syph. **40**:249 (Aug.) 1939. Birnberg, C. H., and Rein, C. R.: Treatment of Acne Vulgaris: A Preliminary Study on the Value of Pregnant-Mare Serum, J. Clin. Endocrinol. **4**:65, 1944. Ingram, J. T.: Acne Vulgaris, Practitioner **152**:304, 1944. Mitchell-Heggs, G. B.: Acne Vulgaris and Its Treatment, ibid. **157**:379, 1946. Forman, L.: Acne Conglobata Treated by Implantation of 300 Mg. Stilboestrol, Brit. J. Dermat. **60**:333, 1948. Goeckerman, W. A.: Hormonal Therapy of Acne Vulgaris in the Female, Arch. Dermat. & Syph. **61**:237 (Feb.) 1950. Way, S. C., and Andrews, G. C.: Hormones and Acne, ibid. **61**:575 (April) 1950.

38. Sulzberger, M. B.; Addenbrooke, E. F.; Joyce, S. J., Greenberg, S., and Mack, A. G.: Tropical Acne, Medical Bulletin 46, United States Navy Department, 1946, p. 1178; Tropical Acne, Bulletin 6, United States Army Medical Department 1946, p. 149. (*a*) Novy, F. G., Jr.: Tropical Acne, California Med. **65**:1, 1946; (*b*) A Severe Form of Acne Developing in the Tropics, Arch. Dermat. & Syph. **60**:206 (Aug.) 1949.

character of the eruption, including the presence of double comedones, distribution, severity, and age incidence, coincided with that of acne conglobata. Although, as Novy stated, it resembled acne conglobata in all these features, he did not consider it a variant of this disorder because of its rapid evolution and involution to climatic response. In his series of patients, 98 out of 100 gave a history of previous acne, whereas in those reported by Sulzberger, the incidence was 27 out of 51 patients. These studies seem to suggest that in the development of the more fulminating types of acne a change in environment from a temperate to a tropical climate is only a precipitating factor in susceptible persons.

Since the introduction of corticotropin (ACTH) and cortisone in the treatment of a variety of diseases, one of the unfavorable complications has been the development of acne. This untoward reaction, following the administration of the masculinizing steroid hormones, affords an opportunity to study the genetic and hormonal background of this group and to determine whether or not they present a previously disturbed pilosebaceous mechanism.

Despite the accumulation of increasing evidence that a hormonal effect exists, the therapeutic management of acne by this means alone affords only occasional or partial benefit. The value of hormonal therapy apparently decreases as the severity of the acne increases; however, the effect of the hormones on the apocrine and sebaceous secretions is most likely the necessary prelude to bacterial invasion in the development of the more severe variants of the acne process.

THE ROLE OF INFECTION

Emphasis has been placed repeatedly on the significance of bacteria in the development of the severe forms of acne. Unna,[39] in 1893, described the acne bacillus, and he attached considerable importance to the role of a micro-organism in the production of the comedo and in the development of the acne process. Since that time, following the work of Sabouraud and others, of the multitude of micro-organisms which have been identified none has received general acceptance by discriminating observers. Bacteriologic studies of the severe forms of acne disclose a large variety of organisms, of which variants of the micrococci (staphylococci) are predominant. Many of these organisms constitute the natural flora of the skin, and undoubtedly there are other factors which play a role in their pathogenetic significance. In this connection, there is the interesting phenomenon of the spontaneous involution of tinea capitis at the time of puberty, which may be associated with alteration in the balance of the sex hormones, or other factors which modify the terrain, thus inhibiting growth of the specific organism.

Fleming [40] claimed to have produced pustules on the forearm of a patient with acne by rubbing a broth culture of the organism on the skin, but he was unable to reproduce this reaction in a patient without acne. Goldsmith [41] minimized the importance of the presence of bacteria. He has never been able to produce acne lesions in man by rubbing cultures of the acne bacillus on the skin. In a study of

39. Unna, P. G.: Histopathology of the Diseases of the Skin, translated by N. Walker, New York, The Macmillan Company, 1896.

40. Fleming, A.: On the Etiology of Acne Vulgaris and Its Treatment by Vaccines, Lancet **1**:1035, 1909.

41. Goldsmith, W. N.: Recent Advances in Dermatology, London, J. & A. Churchill, Ltd., 1936, p. 472.

acne conglobata, Belote [12] was able to produce a pustule in one patient from pus from another but was unable to reverse the process. Lynch [22] has shown that the inflammatory reaction can arise without apparent rupture of the follicle and without demonstrable bacterial invasion of the follicle wall, the glands, or the connective tissue.

All evidence points to the significance of the formation of the comedo and the resulting impaction of the hair follicle, rather than to the infection as having a primary role. Bacterial invasion can be considered a late sequela in the course of the severe acne process. These disorders are not the result of a specific organism. The significant factor is the nature of the soil of the person and his abnormal ability to react.

SUMMARY

The correlation of hidradenitis suppurativa, acne conglobata, and dissecting cellulitis of the scalp and neck in clinical characteristics and pathologic physiology and anatomy is discussed. An appraisal of the genetic, hormonal, and infectious elements is presented.

The similarity of the apocrine and sebaceous glands in their embryologic, cytologic, anatomic, and physiopathologic components is emphasized.

It appears that the initiation of the acne process depends upon a disturbance of the hormonal balance in addition to the inherited susceptibility of the patient. The significance of the role of bacteria in the development of the severe variants of acne is minimized.

In this presentation I have devoted my attention chiefly to what is known about the acne process. What is not known is of equal significance, for example, the fundamental mechanism in the production of hyperkeratinization of the follicular orifice and the relationship of hormonal stimulation. These are but a few of the obvious gaps in our present-day knowledge.

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ABSTRACT OF DISCUSSION

DR. FRANCIS W. LYNCH, St. Paul: Dr. Brunsting has reviewed an interesting series of disorders, clearly pointing out their similarities, but in the final attempt to align them we have little solid material to grasp. Aside from inherited variations in seborrheic function, which are rather common, the genetic factors are evident only in acne vulgaris, and none too clear even there. Hormonal disturbance is clearly evident only in acne vulgaris and is only vaguely suggested elsewhere. Bacteriologic study has given no positive etiologic information. We are left to conclude that these disorders are of unknown cause, occurring in adults who have some degree of seborrhea, and manifested by purulent inflammation beginning periglandularly but spreading to form abscesses and healing with formation of peculiar scars.

Attempting to clarify my thinking, I tabulated the occurrence of many clinical features of this group and came to the following conclusions, simplified at some cost to accuracy:

	Acne Vulgaris	Acne Conglobata	Dissecting Cellulitis	Hidradenitis Suppurativa
Site	Sebaceous gland	Sebaceous gland	Sebaceous gland	Apocrine gland
Comedos				
Single	+	+	−	−
Double	−	+	+	+
Papules	+	+	±	−
Cystic papules	+	+	−	+
Abscesses				
Discrete	+	+	±	+
Dissecting	−	+	+	+
Scar bridges	−	+	+	+
Sebaceous cysts	+	+	−	−
Sex predominance	Equal	Male	Male	Equal

Reviewing these incomplete and not entirely accurate data one finds that acne conglobata shows practically all the features of acne vulgaris but with exaggeration and without clear evidence of endocrine imbalance. The patient looks old and tired, and his infections are not effectively localized but are not massive or overwhelming. The difference, then, is in the make-up of the patient. Perhaps the pituitary overreacts due to adrenocortical failure, aging the patient but stimulating the testicular androgens and thus continuing the picture of acne. Possibly this explains the occurrence of the disease only in males.

The patient with dissecting cellulitis is usually a clearly masculine male, but acne, if present, is slight. His difficulty is due to subepidermal and subcutaneous spreading of a pyogenic infection on the neck and scalp, areas notoriously unable to withstand bacterial attack, as evidenced by the frequent occurrence of folliculitis, furuncles, and even carbuncles. This disease could be a regional pyoderma with no more evidence of acne than might accompany slight to moderate seborrhea, and one without endocrine implications.

Hidradenitis, too, appears to be chiefly a regional rather than a systemic disease. Excised adequately it does not recur. Mild cases have little if any resemblance to acne vulgaris or conglobata. Only when the disease is extremely prolonged and extensive does the patient tend toward cachexia and then show some of the features of acne conglobata. Endocrine implications are suggestive rather than definitive.

In his review Dr. Brunsting has clearly pointed out the positive correlations in this group of diseases. There is no doubt that such similarities exist, but if we emphasize them we may forget the differences, which may yet prove to be the more important. For the present I would prefer to regard acne conglobata as the coexistence of ordinary acne and pyogenic infection, in a host somehow peculiar, and to regard dissecting cellulitis and hidradenitis as pyogenic diseases having slight resemblance to acne and resulting chiefly from some as yet unclear regional, structural, and functional pathologic process, though obviously also with some systemic pathogenetic features.

Dr. Stephen Rothman, Chicago: The paradox in the endocrine constellation in acne lies in the fact that its sex incidence is 1 to 1. Thus testicular hormones certainly cannot be the only responsible hormones. However, if we assume that the adrenocortical steroids are responsible in both sexes, it remains unexplained why prepubertal castrates are entirely free from seborrhea and acne. The acneform eruption appearing in the course of corticotropin (ACTH) treatment is in most cases a papular eruption without black heads and without seborrhea. Planimetric measurements of the sebaceous glands cross sectional areas before and after corticotropin treatment has not yielded consistent results. Whether cortical steroids are operating in the pubertal development of sebaceous glands is still a moot question.

Comparing hidradenitis with acne, I believe there is a very important difference in spite of the similarities of endocrine influences on sebaceous and apocrine glands. Hidradenitis requires infection with pathogenic hemolytic micrococci (staphylococci), whereas acne develops without any such infection.

Dr. Samuel Ayers, Jr., Los Angeles: I should like to offer one suggestion to account for the conglobata type of acne which I suppose others have seen develop in the course of the ordinary acne. It is not uncommon for a person of either sex to have an ordinary common type of acne over a period of months or sometimes years and then suddenly, within a period of several weeks, without any apparent change in environment or anything else, manifest the acute almost-fulminating type of conglobata lesions with large deep abscesses.

I have often thought it represents the development of an allergic reaction to the infecting organisms, in much the same way that kerion develops in the course of some cases of tinea capitis. While I have not conducted any experiments to prove that this has occurred, it has seemed to me that perhaps these deep-seated lesions represent a bacterial allergy to relatively common organisms, such as Micrococcus or acne bacillus; in other words, not an increase of virulence but a change on the part of the tissues. In studying the value of vaccine in arthritis several years ago, Clausen and Allen found that autogenous vaccine administered intravenously apparently not only increased immunity but also offered the best means of decreasing sensitivity of the tissues to the organism. We have felt that the use of autogenous vaccines intravenously, in a dose sufficient to avoid severe systemic reactions, along with other accepted methods of

therapy, gave good results in acne conglobata and in some cases of hidradenitis, as well as in chronic recurring furunculosis.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: I agree with the thesis that these diseases are varied manifestations of the same systemic abnormality, namely, the acne process, which is an inherited characteristic. Some persons may show only one phase of the disease, others, all three. Careful examination of patients with hidradenitis or with so-called dissecting cellulitis of the nucha and scalp will often reveal signs of old or active acne elsewhere, in the form of oily skin, pitted scars, impacted cysts, or multiple comedones. Hidradenitis of the axillae alone is frequently associated with double comedones.

I believe, too, that the importance of the element of infection, even in the advanced stages of the disorder, has been overemphasized. Multiple abscesses and extensive burrowing sinuses may occur, but still the lesions are indolent, for the most part, and systemic reactions are minimal, except for general debility in some cases. When antibiotics are administered, the beneficial effects are temporary, as would be expected in any type of infection characterized by impaction, as, for example, in pulmonary empyema.

Hormonal influences in acne are not well-defined; most of the evidence on that score is presumptive. So far the laboratory has been of little help. If any measurable abnormalities are to be found, certainly they should appear in persons who present the combination of these three phases of the acne process at its worst.

DR. RICHARD L. SUTTON, Kansas City, Mo.: Acne has been of considerable interest to me for a number of years. In our 10th edition (Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939, p. 437) we wrote, regarding acne conglobata, "We cured one patient to the point of complete healing with healthy scars in two months by means of low fat diet and thyroxin, the dose of which was guided by the basal temperature." Acne conglobata, when located mainly in the perianal region, has been called "perianal pyoderma." Collaborating with Mark Marks (Sutton, R. L., Jr., and Marks, M. M.: Acne Conglobata and Perianal Pyoderma [Hidradenitis Suppurativa], *J. A. M. A.* **121**:1344-1347 [April 24] 1943), we described this identity.

In our 10th edition of "Diseases of the Skin" we also wrote: "Two diseases, in our opinion, are confused under the current title, 'hidradenitis suppurativa.' The first is acne of the apocrine glands, and the second is pyogenic infection of apocrine glands, which is often secondary to the first." These two types of aprocrine adenitis are clinically distinct. In one, a straightforward entity, the person has furuncles under the arms. In the other, the acne lesions form corded and xanthoma-like scars, which drain chronically and which are not responsive to treatment appropriate for simple pyogenic infection.

There are many facts about acne so apparent to the clinician that they seem to require no further proof than the observation. For example, you do not catch acne. If you spend hours over periods of years doing the minute surgery of removing comedones and evacuating pustules, you do not infect your fingers. You can put a relatively "dirty" scalpel into a comedo, and you do not start something there. If you get the comedo out neatly, you prevent the initiation of pustulation. However, if you crush the comedo so that its waxy material is dispersed within the mesoderm, then you produce a vigorous inflammatory reaction. Thus acne has nothing to do with infection. The patient himself knows he must not crush a comedo; he finds that out the hard way.

If in acne you could get the oil glands small and empty, there would no longer be disease. I am sure that milk is harmful in acne and the abstinence from milk helpful. The clinical experiment is straightforward: Prescribe for your acne patient the ingestion of considerable milk and see what happens. However, withholding milk is inadequate to cure the patient. I strongly suspect that skimmed milk free from its butterfat is about as harmful as whole milk, and I suspect that there is a hormone in milk that influences sebaceous glands of the human being. Milk comes from a modified sebaceous gland. In endeavoring to test such a hypothesis, one gets no help from the Dairy Council, which is economically dependent upon the thesis that milk is an essential of the diet, to be sold in large quantities.

The acne patient is usually tired, without knowing why. This is not necessarily suggestive of adrenal deficiency. Thyroid is a chemical that corrects the tired feeling of many human beings. Some of us in this audience believe that thyroid helps acne, while others do not believe

it. I suspect that the latter have not tried thyroid or possibly have not tried it with skill. The correct use of thyroid requires some clinical finesse. In determining the dose, many internists disregard basal metabolism tests, and so do I. I give an acne patient thyroid and observe his response. If the dose is not enough, it does nothing at all. If the dose is just right, the tired feeling disappears: The patient, who heretofore had no interest in breakfast, becomes hungry for breakfast, she has a lighter step and is better and brighter; her parents note the difference, and her face improves. If the dose of thyroid is too large, overdosage symptoms are perfectly apparent to an alert clinician.

To get the oil glands small and empty, it seems to me that direct efforts include a diet relatively low in fat but otherwise completely adequate, thyroid in appropriate dosage—and I beg those of you who have not used it to try it—x-ray therapy which damages the glands so that they cannot secrete, and minute surgery, which is tiresome and which does require a respectable amount of skill. Other efforts are superfluous, for medicines put upon the surface of the skin accomplish little indeed, and you certainly cannot wash the disease away.

I am delighted to hear at last recognition of the fact that hidradenitis of the acne type and acne conglobata are variants of acne.

Dr. Paul E. Bechet, Elizabeth, N. J.: I have always been interested in the different clinical phases of the conglobata type of acne and have observed the occasional development of a psychosis from the extensive, disfiguring scarring on the back and chest, thereby interfering in necessary athletic pursuits. I have noted it more frequently in men than in women, and most frequently in the over-tall, rather-thin adolescent of the blond type, with an occasional secondary anemia.

X-ray therapy is almost specific, but the adjuvant use of hematinics accelerates recovery. They can be administered by mouth or parenterally, depending on the degree or type of the anemia, and in addition to the usual penicillin or sulfonamide therapy.

Dr. Norman N. Epstein, San Francisco: I am of the opinion that secondary infection is of considerable importance in the production of the severe types of acne vulgaris. This is borne out by the effects of the antibiotics when administered internally in acne. My experience is similar to that of Andrews who reported the satisfactory control of resistant pustular acne by the use of antibiotics. The judicious use of these remedies alters the course of acne very definitely.

Dr. William H. Goeckerman, Los Angeles: Dr. Brunsting has presented us essentially with a thesis. While, of course, there is much discussion that can be brought to bear on it, I should like to support his concept particularly strongly, because I think it has not received the support it deserves. I think, if we are going to make any real progress in this affliction, it is this concept that we have to accept. Summing it up in a few words it is this: The patient has a certain type of skin, an oily skin of the acne type, and on top of the skin a secondary infection develops, whether it is a Micrococcus or Streptococcus infection of a certain species in this instance is not of great importance.

Harking back to some of the other discussions, the best results in these patients are obtained by using the right endocrine to improve the acne, and then in addition using one of the antibiotics to counteract the infection.

My experience with males is not large, and I do not believe that the male hormone is particularly significant here. In my experience with females, however, the estrogen is of utmost importance, and I am not thinking in this connection of the adrenal gland or possibly of the ovary, because estrogens do much more than just affect the sexual and endocrine organs. They affect the stomach, the pancreas, and probably the liver. We are dealing with what might be called, in general, a very great tonic effect. Where does this secondary infection come from? We do not know whether from an internal or external source, but in this particular instance, while I am not a great proponent of focal infection in many other conditions, I believe that we must never overlook the possibility that this type of patient may have some secret, some obscure focus of pyogenic infection.

Dr. Fred D. Weidman, Philadelphia: Dr. Brunsting has discussed genetics, hormones, and the infectious elements in this disease, and I should like to introduce one more factor, namely, the chemical element. It is a matter of record even in the older textbooks on histologic

chemistry that lecithin can be acted upon by bacteria to produce choline. The latter is a violently toxic substance of the order of histamine. All of us know the flare that develops upon squeezing an acne pustule and that it is not commensurate with the amount of trauma; it is something like a histamine flare in miniature. Of course, in an acne lesion the appropriate fatty material is present, with lecithin as one of its fatty degenerative products, and bacteria are omnipresent. Such a mechanism may serve to bridge the discrepancy noted in certain acne lesions, namely, that they do not appear to be bacterial but are due possibly to some different factor, as, for instance, choline.

In recent years the experimentalists have discovered a method of producing cirrhosis of the liver by withholding choline. (Hartroft, W. S.: In Vitro and in Vivo Production of a Ceroid-like Substance from Erythrocytes and Certain Lipids, *Science* **113**:673 [June 15] 1951.) In connection with this, a certain brown pigmentary degeneration develops that is called ceroid. Now, it is a fact that in apocrine sweat glands ceroid is normally present, although in minute quantities; it must be a part of their metabolism, and after that there may be a relationship between the ceroid in these glands and that which appears in cirrhosis of the liver. In short, abnormal metabolism of lipid-lecithin-choline opens up possible relationship between hepatic and sebaceous function on the one hand, and ceroid degeneration becomes a factor linking liver and apocrine glands.

Dr. Henry A. Brunsting, Toledo, Ohio: It is inevitable that a difference of opinion occurs when one uses various factors as a common denominator in grouping disorders previously described as separate entities. In a paper of this scope it is impossible to include all the factors that may play a role in the acne process. Emphasis has been placed previously on the significance of diet, vitamins, water-balance, psychic factors, and choline metabolism as discussed by Dr. Weidman. Some of these may be influenced by hormonal imbalance. I disagree with those who believe that the incidence of associated acne vulgaris is low in patients with hidradenitis or dissecting cellulitis. In this paper I avoided using the term "pyoderma," which I believe should be reserved for those diseases in which the infectious element is of primary causative significance. In the advance of our knowledge we should study the patient and the acne process as a whole and not consider each disorder as a separate regional cutaneous disease.

MEDICAL ASPECTS OF HOME COLD WAVING

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SINCE the introduction of cold-wave preparations for home use in 1945, consumer usage has increased year by year, reaching a figure of some 37 million in 1949. As the agents used in the cold-wave process contact hair and skin, the subject becomes of direct interest to dermatologists. The purpose of this report is to examine the basic theoretical principles, materials, and techniques employed in the cold-wave process, primarily to clarify the mechanisms through which reactions of medical or medicolegal importance may develop. Figures obtained from the files of a manufacturer of home cold-wave products have been used to evaluate the frequency of these reactions. Previous reports have, in general, cited only isolated case histories of patients with some dermatologic or systemic manifestation allegedly associated with the use of cold-wave preparations, so that it has been difficult to obtain a clear concept of the causes, characteristic features, or frequency of occurrence of reactions.

Although permanent waving was first developed on an empiric basis by Nessler as long ago as 1906, the cold-wave process became possible only as the result of recent investigations into the physical and chemical structure of hair keratin. These studies have shown that human hair as well as certain other animal fibers are filaments composed of elongated polypeptide chains, lying roughly parallel to the long axis of the hair. In hair keratin these polypeptides are attached to adjacent ones by side chains, building up polypeptide "grids."

X-ray diffraction studies of hair keratin [1] indicate that the polypeptide grids exist in a regularly buckled or folded form, stabilized in this form as the result of stresses exerted on the polypeptide chains by the attached side chain linkages. If the behavior of hair fibers in the wet and the dry state is examined, mechanisms basic for permanent waving can be illustrated. When tension is exerted on a hair, the folded polypeptide grid is straightened out, and the hair therefore elongates, returning to its original stable folded form and to its original length when the tension is released, if the elastic limits of the hair have not been exceeded. If the hair is first wetted, it stretches more readily, since water acts to decrease the stresses exerted by the side chains which hold the polypeptides in their folded form. The elongated wet hair rapidly returns to its original length when tension is released; if, however, the hair is dried in its new form, it returns much more slowly unless rewetted. This phe-

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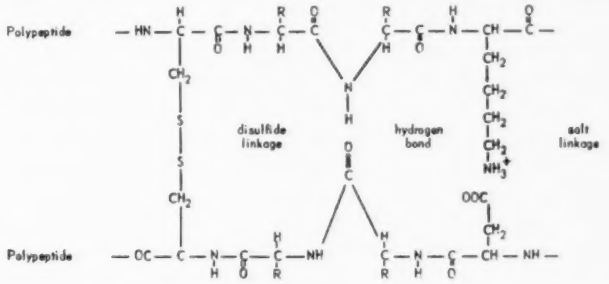
1. Astbury, W. T., in Savill, A. F.: The Hair and Scalp, Ed. 3, Baltimore, William Wood & Company, 1945, p. 62.

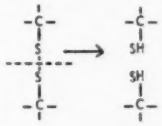
nomenon is a familiar one, and is the basis for temporary "setting" of hair with water, as in the straightening of disordered hair by wetting and brushing, or in pin-curling.

To develop a more permanent "set" or change in configuration it is necessary to use heat, alkalies, or reducing agents in addition to water. With these agents, some of the cross linkages binding the polypeptides are actually released, and, if at the same time stress is exerted on the hair fiber until the side-chains reattach, this reattachment will occur at new sites. The newly formed linkages are fairly stable, so that the hair maintains its new configuration for a long period, even if rewetted frequently. If, at the time the cross linkages are freed, greater stress is applied to



the fiber on one of its sides than on the other, its new form will then be curved, or "waved." In the actual practice of permanent waving this result is brought about by wrapping a strand of hair fibers around a rod of small diameter, stretching the outer surface while compressing the inner face of the fiber in each spiral formed.

In so-called "hot waving," heat (developed either electrically in machine waving, or with chemical heating pads in machineless waving) is used to strengthen the action of borax, sulfites, and alkalies. In cold waving, thioglycolate salts are used at room temperatures.[2] Thioglycolates penetrate the hair readily, and are capable of reducing disulfide cross linkages to the free –SH form.



After initial reduction of the disulfide linkages, the hair fiber is put in the desired curvature; stable reattachment of cross linkages in their new positions is ensured by the use of oxidizing agents ("neutralizers"), which convert free –SH back to S–S linkages and also neutralize residual excess thioglycolate.

Almost all home cold-wave solutions employ ammonium or sodium thioglycolate, or mixtures of the two salts, in aqueous solution. Concentration of thioglycolate ranges from 5.5 to approximately 7%, with the pH raised to 9.0 to 9.5 by addition of ammonium or sodium hydroxide. So-called "professional" or beauty-shop cold-wave solutions have similar compositions, but with a substantially higher concentration of thioglycolate and alkali. With some variation, depending on the particular manu-

2. Thioglycerol and ammonium hydrogen sulfide have been proposed as cold-waving agents, but have been discarded because of toxicity problems.

facturer, wetting agents, resinous or oily creaming agents, and perfumes are added to the wave solution to enhance its efficiency or acceptability to the consumer.

Typical directions for carrying out a home cold permanent wave are as follows: The hair is first shampooed to remove sebum or oily hair dressings which may interfere with penetration of the waving agent. The hair is then sectioned into some 40 tresses, and each is wetted with the thioglycolate solution. A small square of paper ("end paper") is folded over the distal end of the tress to facilitate handling, and it is then rolled up on a plastic or fiber curling rod and resaturated with wave solution. The subject then takes time checks on test curls at intervals, removing the curling rod and examining the wave pattern produced. The time required may be as much as two hours, depending on the thioglycolate concentration and pH of the waving lotion, the diameter of the hair fibers, the cuticle-cortex ratio, tightness of winding on the curling rod, temperature, the tightness of the wave desired by the consumer, and other factors which will be discussed. When the proper amount of curl is obtained, the neutralizer solution (generally sodium or potassium bromate or sodium perborate) is applied to each tress, the curlers are removed, and rinsing with neutralizer and water is again carried out. As a final step, the remoistened hair is put up in pin-curls to create the desired style.

Reactions known or claimed to occur after this relatively simple operation may be divided into the following categories: cutaneous, hair alteration, ocular, and systemic.

CUTANEOUS REACTIONS

Dermatitis following use of cold wave solutions has been reported by Cavigneaux and his associates,[3] Cohen,[4] Goodman,[5] Howell,[6] McGill and Ray,[7] Cotter,[8] Beek,[9] Goldman,[10] and Bellach.[11] Analysis of these case reports suggests that the disorders may be divided into three groups: (1) primary irritant dermatitis, (2) allergic eczematous contact dermatitis, and (3) dermatitis due to causative agents other than cold-wave solution. However, because of the inadequacy of the data furnished, it is difficult in any individual case to place the condition in one or another of these categories. In some cases, the dermatitis occurred on the hands of professional beauticians who were exposed repeatedly to a wide variety of irritants and sensitiz-

3. Cavigneaux, A.; Charles, A.; Fuchs, S., and Tara, S.: L'Épidermo réaction des dermites artificielles des "Permanentes à froid," Arch. mal. profess. **10**:59, 1949.

4. Cohen, M. H.: A Clinical Appraisal of the Cold Wave Process, Arch. Dermat. & Syph. **60**:14-23 (July) 1949.

5. Goodman, H.: Dermatitis from Cold Wave Permanent Chemicals, Urol. & Cutan. Rev. **49**:117-119 (Feb.) 1945.

6. Howell, J. B.: Contact Dermatitis from Cold Permanent Waving, Arch. Dermat. & Syph. **49**:432 (June) 1944.

7. McGill, C. M., and Ray, L. F.: Cold Wave Dermatitis: Report of 2 Cases, Indust. Med. **16**:238 (May) 1947.

8. Cotter, L. H.: Thioglycolic Acid Poisoning in Connection with the "Cold Wave" Process, J. A. M. A. **131**:592-593 (June 15) 1946.

9. Beek, C. H.: Eczema Caused by Thioglycolic Acid Used in "Cold Wave" Process, Nederl. tijdschr. geneesk. **91**:2500-2502 (Sept. 6) 1947.

10. Goldman, L.; Mason, L., and McDaniel, W.: Permanent Wave Process, J. A. M. A. **137**:354-357 (May 22) 1948.

11. Bellach, H.: The Effect of Home Permanent Wave Preparations (Ammonium Thioglycolate and Potassium Bromate) on Hair, Connecticut M. J. **14**:405-411 (May) 1950.

ing agents.[10] Goodman [5] suggested that hand dermatitis in beauty operators, believed due to thioglycolate, was always "toxic" rather than allergic in nature, since the reactions to patch tests with the wave solution were negative in all his cases. McGill and Ray,[7] in reporting two cases of contact dermatitis believed due to cold-wave solution, found one negative reaction upon patch test; the other was not tested. Two cases reported by Cotter had positive patch-test reactions (? to thioglycolic acid).[12] What proportion of these patch-test-negative conditions actually were due to waving solution cannot be determined, since shampoos, wave-setting lotions, special rinses, dyes, etc., used in conjunction with the waving process were generally not investigated as possible allergenic or irritant agents. In Howell's case, patch tests showed the allergen was actually a special preparatory lotion rather than an essential ingredient of the waving solutions.[6]

Under conditions of normal use the average home cold-wave solution cannot be classified as a primary irritant. Personal observation in approximately 1,000 subjects disclosed no instances in which there was any reaction more severe than mild transient erythema of the scalp, forehead, or neck after the completion of the wave. Ninety-minute contact tests with aqueous ammonium thioglycolate of average waving strength also failed to produce any reactions greater than momentary erythema.[13] Similar findings were reported by McNally and Scull.[14] They applied a 6.5% ammonium thioglycolate solution for 40 to 60 minutes to the skin of 154 subjects daily for a period of two months, with no resultant reaction. Goldman found two reactions in 83 subjects by means of a "streaking test" when wave solution was applied to the scalp, none when applied to the forehead.

Although, as this evidence indicates, home cold-wave solutions are not primary irritants under conditions of normal use, irritant dermatitis following their use can occur. Such reactions are generally traceable to deviations in the method of application which enhance the keratolytic potentiality of the solutions. In some instances an impermeable cover, such as a plastic or waxed-paper cap, is used after application of the thioglycolate solution. Evaporation of ammonia and air oxidation of thioglycolate is thereby slowed, and since the effective concentration of the waving solution is then maintained at a higher level for a long period, potential irritancy increases. (When evaporation is allowed to proceed normally, the pH of the thioglycolate-wetted hair tress falls rapidly from 9.3 to approximately 8.2.) In some instances the waving solution is used overgenerously, puddling behind the neck and ears, and is then held in close contact with the skin by a towel wrapped turban-fashion around the head. Antecedent or concurrent damage to the scalp skin, such as inflammatory dermatoses, shampooing with strong detergents, friction of massage, and exposure to high temperatures in drying the hair, may also predispose to irritant reactions. Occasionally, the wave solution is left on overnight without rinsing, or the suggested method of neutralization is incomplete. Irritant

12. Thioglycolic acid is a primary irritant in even low concentrations.

13. When the concentration of thioglycolate and free ammonia in the waving solution was increased from the normal level of 0.5 N and 0.525 N, respectively, to 0.907 N and 0.912 N, five of forty-nine subjects showed erythematous test reactions lasting up to 12 hours. Stronger "professional" cold-wave solutions, on this basis, are perhaps to be considered threshold primary irritants.

14. McNally, W. D., and Scull, R. H.: Thioglycollate Cold Wave Process, Arch. Dermat. & Syph. **57**:275-278 (Feb.) 1948.

dermatitis of the hands from home cold-wave solution is seen mainly after repeated contact without protection of the hands, as in "semipros," women who give one or several home waves weekly to friends or relatives. In these subjects, an ordinary "housewives' eczema" due to detergents may become exacerbated, or a more characteristic picture may be seen in which there is maceration and exfoliation of the skin of the thumb and forefinger bilaterally, due to mechanical trauma incident to rolling up the plastic curlers while the skin is wetted with waving solution.

During a period covering one million unit sales of one manufacturer's home cold wave product, there was a total of 22 complaints of cutaneous reactions, 17 of which were probably external irritant dermatitis, including 3 cases of hand dermatitis. Of the four reactions finally classified as allergic eczematous contact dermatitis, patch tests showed thioglycolate itself was the offender in two, and neutralizer (sodium bromate) in one. There was one case in which generalized urticaria developed, perhaps as the result of percutaneous absorption in an anaphylactically sensitive person. Unfortunately it was impossible to perform confirmatory tests on this subject to determine whether waving agents were the actual allergens. In other series covering several million sales, there were similar percentages of irritant and sensitization reactions, including shampoo, hair-dye, and hair-rinse reactions, and one case of erythema multiforme in which the causative agent could not be ascertained. There were also occasional reports of exacerbation of preexistent dermatoses, such as folliculitis and seborrheic dermatitis. At the present writing, it is difficult to assay properly the importance of cold-wave solutions in causing aggravation of such eruptions. There is some evidence that it may be possible, and most manufacturers warn the consumer against use of cold waves when there is any abnormality of the skin.

Indications that the low incidence of true allergic eczematous sensitization to thioglycolate shown by the complaint figures is not misleading were found in an experimental investigation of the sensitizing potential of another mercaptan proposed for use as a cold-waving agent. It was found possible by the technique used to eczematously sensitize 40% of normal subjects with the new mercaptan, while none of 25 subjects could be sensitized to thioglycolate. The new product had been used as a waving agent in 250 persons without reaction, 30 of the subjects having had two waves. Further evidence of the low-sensitizing potential of thioglycolate was furnished by McCord [15] and by Behrman and others.[16] In repeated patch tests on 162 persons, McCord observed no positive response in the absence of a like initial reaction. Behrman, in a similar study on 109 subjects, using paired patch test, found two weak reactions on retests, one of which was later shown to be negative. He also reported that of 390 factory workers handling thioglycolates, 0.26% showed positive reactions. One of the reactors was under constant daily exposure to thioglycolate and yet had experienced no difficulties; the other had had five cold waves without the appearance of any dermatitis and may therefore have had a false-positive patch-test reaction.

15. McCord, C. P.: Physiological Properties of Thioglycolic Acid and Thioglycolates, Indust. Med. **15**:669-676 (Dec.) 1946.

16. Behrman, H. T.; Combes, F. C.; Weissberg, G.; Mulinos, M. G., and Hurwitz, M. M.: The Cold Permanent Hair-Waving Process, J. A. M. A. **140**:1208-1209 (Aug. 13) 1949.

ALTERATIONS IN THE HAIR

Hair damage after cold waving has been the subject of reports by Reiches and Lane,[17] Bellach,[11] Sidi,[18] Rabeau,[19] Tournaine and Gallerand,[20] and Michel and Saint-Paul.[21] As in the case of irritant reactions, consideration of quantitative differences between home cold-wave and professional-strength solutions, and the role of other agents applied to the hair are all-important factors in evaluating the reactions described by these authors. Except for the report of Bellach, all the articles cited refer to hair damage following use of higher concentrations of thioglycolate, such as employed in beauty-shop cold waves. It should be recalled that release of disulfide linkages, application of mechanical stress, and subsequent neutralization to effect recombination of disulfide linkages in their new positions are the basic mechanisms in waving. Thus, concentration of active agents, time of action, amount of physical strain on the fiber, adequacy of neutralization, and condition of the hair itself are the variables which will influence the final outcome. With present-day home cold waves, directions to the consumer recommend limits on tightness of winding and duration of application of thioglycolate and neutralizer, which have been shown will safely wave "normal" hair. If the hair is abnormal, or if there are serious deviations from directions, it is possible for hair damage to occur, although there is remarkable latitude as regards limits of safety.

Under conditions of normal use some 20 to 30% of the total cystine (disulfide-linked amino acid) in hair keratin is reduced during the home cold-waving process; with neutralization, there is substantial restoration of disulfide linkages. Concurrent with the changes in cystine content, there are variations in the ultimate breaking strength and 20% indices[22] of the fiber. During the preneutralization stage of thioglycolate action there is diminution in these values, but almost complete restoration of strength and elasticity of the hair fiber following application of neutralizer and chemical rebuilding of cystine linkages can be demonstrated as shown in the following tabulation[23]:

	Cystine	Ultimate Strength, Gm./Cm.^{2}	20% Index
Untreated hair	15.8-16.2	15.4-17.1	.....
Thioglycolate treated hair (maximum change)	14.2-14.6	.....	0.4-0.5
Thioglycolate treated and neutralized hair	15.8-16.2	15.5-16.2	0.8-0.9

When concentration, time, temperature, etc., are held constant, differences in the tightness of wrapping on the rod will produce greater or less curl, and if the hair fiber is overstretched through excessively tight winding, decrease in tensile strength

17. Reiches, A. J., and Lane, C. W.: Temporary Baldness Due to Cold Wave Thioglycolate Preparations, J. A. M. A. **144**:305-306 (Sept. 23) 1950.

18. Sidi, E.: Les accidents provoqués par le nouveau procédé dit permanente à froid, Gaz. méd. de France **53**:499 (Sept.) 1946.

19. Rabeau, H.: Au sujet des ondulations à froid, Ann. dermat. et syph. **7**:210-211 (June) 1947.

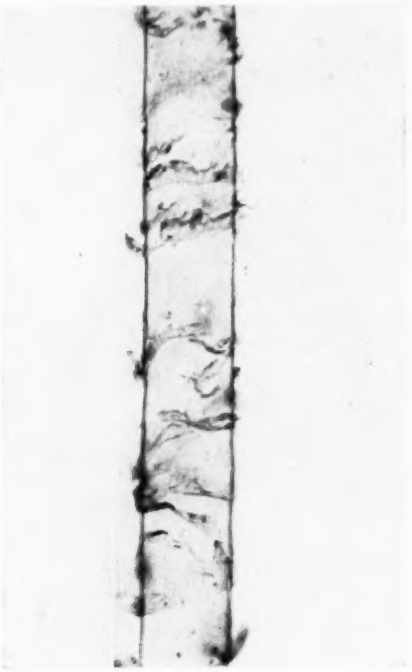
20. Touraine, A., and Gallerand, L.: Trichoclasie en larges plaques après "défrisable" à froid, Ann. dermat. et syph. **7**:209-210 (June) 1947.

21. Michel, P. J., and Saint-Paul, J.: Les dangers des "permanentes à froid," Ann. dermat. et syph. **7**:224 (June) 1947.

22. The 20% index is the ratio of the energy required to cause 20% extension of the fiber after chemical treatment to that required prior to such treatment.

23. Danehy, J.; DenBeste, M., and Jensen, C.: Unpublished data.

may result. Failure to neutralize, with consequent inadequate restoration of cystine linkages, may also contribute to weakening of the hair fiber. If the hair has been bleached, or dyed with paraphenylenediamine dyes (which use hydrogen peroxide to oxidize and fix the dye), permanent alterations in the hair are known to occur which interfere with normal wave processing. Hydrogen peroxide damages hair cuticle (Fig. 1), probably increasing the speed of penetration of applied thioglycolate, and in addition produces some irreversible oxidation of disulfide linkages in the keratin of the cortex. Women with bleached or dyed hair are therefore warned of the danger of "overprocessing" with cold-wave solution, and in some



Hair cuticle damaged by hydrogen peroxide.

instances manufacturers supply a solution of lower concentration for use on such damaged hair. Overfrequent waving (more than three or four times yearly) may also weaken the hair, particularly in women past 60, in whom the rate of growth of long hair has practically stopped, so that the same segment of the hair shaft is waved again and again and is eventually weakened.[24] It also seems probable that overexposure to sunlight may cause alterations in hair which predispose to damage

24. The values in the tabulation apply to hair treated as in the practice of permanent waving. If the hair is actually immersed in an excess of thioglycolate, as in the experiments cited by Bellach, much more rapid and greater cystine reduction is obtained, with concurrent decrease in fiber strength. Under such immersion conditions, there is as much reduction of cystine linkages in 2 minutes as in the presently recommended 90 minutes in the waving procedure.

following cold waving, since Smith and Harris [25] have shown that some disulfide bonds in wool keratin (which is similar in composition and structure to human hair) undergo irreversible oxidation with ultraviolet irradiation.

In actual practice, the dermatologist may be called upon to investigate cases in the following categories: (1) patchy hair breakage, (2) diffuse hair breakage, (3) abnormalities in hair texture, or (4) abnormalities in color or odor. Patchy hair breakage, as illustrated in the report of Reiches and Lane, may result from excessively tight winding of the tress on the rod. (As noted in the preceding tabulation, during the preneutralization stage of waving the breaking strength is temporarily lowered.) Loss of hair may be apparent immediately, and is often accompanied by dermatitis limited to the portion of the scalp corresponding to the damaged tress. Acute external irritant dermatitis of this type is known as a "pull burn" among cosmeticians.

Diffuse hair loss may result from overprocessing in bleached or otherwise damaged hair when failure to follow directions results in overprocessing, and it is occasionally seen following a severe eczematous dermatitis of the scalp. As in the case of patchy hair loss, examination of the fallen hair shows that breakage, rather than excessive fall from the roots, is the cause of the hair loss except in the hair fall which may sometimes accompany severe eczematous dermatitis of the scalp, regardless of the nature of the allergen. Abnormalities in hair texture are due to similar causes, differing only quantitatively from cases in which actual breakage occurs. Thus far, no evidence of hair fall from the roots has been obtained (with the rare exception noted above, when hair fall occurs after severe acute dermatitis). When a fluorescent dye was mixed with the waving lotion, examination under Wood's light of hair fibers plucked from the scalp after completion of waving showed no staining of the hair below a point about 3 mm. above the root, suggesting that the dye-thioglycolate mixture did not penetrate the follicle. Correspondingly, counts of total daily hair combings in a small series of subjects before and after waving showed no increase in the percentage or total number of hairs with attached roots. There is no evidence that the rate of regrowth of hair after breakage is affected.

Discoloration of the hair after waving is seen almost entirely in women with dyed hair. If a paraphenylenediamine derivative has been used, and not completely oxidized, off-shades of color may follow application of thioglycolate. So-called "color rinses" are composites of three or more acid and basic dyes, of a variety of hues including purple, red, green, etc. Some of these colors are more readily extracted from the hair during waving and shampooing than others, leaving the colors of the residual dye.

Abnormal hair odor after cold waving is due basically to inadequate application of neutralizer, so that some residual mercaptan remains in the hair. The odor is particularly noticeable when the hair is rewetted on the first shampoo after the wave, and may be controlled by repeating neutralization.

Complaints of alteration in the hair after waving were received in the proportion of 18 cases per million usages. In over 50% of these cases bleaches or dyes had been used, as shown either by examination of hair samples or by the admission of the consumer. Investigation in the remaining cases revealed a miscellany of causative

25. Smith, A., and Harris, M.: Oxidation of Wool, Am. Dyestuff Reptr. **25**:383-385, 1936.

factors unrelated to waving, including trichotillomania, alopecia areata, toxic postfebrile alopecia, and pediculosis capitis with secondary impetigo. When examination actually revealed damage to the hair, excessively tight winding or other causes producing "overprocessing" were discoverable.

SYSTEMIC INTOXICATION

Reports dealing with the systemic toxicity of thioglycolates have been made by Cotter,[8] McCord,[26] Draize,[27] McNally and Scull,[14] Behrman,[16] Lehman,[28] Smith,[29] and Brunschwig.[30] Brunschwig found that approximately 15% of the methionine in the diet of experimental animals can be replaced with thioglycolic acid. According to Smith, dogs averaging 11 kg. in weight showed no signs of toxicity when fed 2 gm. of ammonium thioglycolate over a two-day period; 5-gm. dosage caused vomiting. Draize applied thioglycolate solution of average waving strength and pH to the skin of rabbits daily for periods up to 90 days, at dose levels of 0.5, 1.0, 2.0, and 4.0 ml. per kilogram. Of 17 animals receiving the equivalent of the "human dose" daily for 90 days (4 oz. [120 cc.] of waving lotion for a woman of average weight), all but 2 survived. Since the solution was inuncted directly to the clipped skin rather than to the hair, allowed to remain without neutralization so that full absorption took place, and was applied to the same areas daily for the specified period, conditions were much more rigorous than those of actual usage in humans. All of 32 animals receiving 0.5 to 1.0 mg. per kilogram per day survived the 90-day test period. At the highest dose level (4.0 cc. per kilogram), 11 of 18 rabbits died. Tissues of 50 animals were examined histologically. There was mild inflammation of the skin, with occasional petechiae, and "only minor visceral changes." Repeated blood examinations during the 90-day period revealed fluctuations in hemoglobin and the hematocrit reading, which were within normal limits. Draize concluded that "the judicious use of these solutions should prove a relatively innocuous procedure."

Similar findings in humans were reported by Behrman. Intensive laboratory studies of liver function, blood chemistry, blood morphology, and kidney function disclosed no abnormalities in 72 factory and laboratory workers in daily intimate contact with waving solutions. Cotter's report gives a different picture of the toxicity of thioglycolates. He stated that thioglycolic acid[31] may produce liver damage after prolonged exposure, particularly in subjects suffering from allergies or anemia. Five cases were cited, in which women with histories of cold-wave

26. McCord, C. P.; Stofer, B. E., and Williams, P.: Action of Thioglycolic Acid and Thioglycolates on Animals After Subcutaneous Introduction, Indust. Med. **1**:62-65 (Feb.) 1947.

27. Draize, J. H.; Alvarez, E., and Whitesell, M. F.: Percutaneous Toxicity of Thioglycolates, Proc. Toilet Goods A. **7**:29-31 (May) 1947.

28. Lehman, A. J.: Health Aspects of Common Chemicals Used in Hair Waving Preparations, J. A. M. A. **141**:842-844 (Nov. 19) 1949.

29. Smith, W. J.: Ueber das Verhalten einiger schwefelhaltiger Verbindungen im Stoffwechsel, Ztschr. physiol. Chem. **17**:459-467, 1893.

30. Brunschwig, A.; Nichols, S.; Bigelow, R. R., and Miles, J.: Sulfhydryl Protection of the Liver, Arch. Path. **40**:81-83, 1945.

31. Thioglycolic acid itself is not in commercial use as a waving agent and per se seems unlikely ever to be.

application had varying symptoms, including anemia, lassitude, nocturia, cramps, gastrointestinal distress, etc. Three of the patients had skin eruptions. In all cases, positive cephalin-cholesterol flocculation reactions were obtained, which Cotter interpreted as indicative of hepatitis due to a chemical poison. In criticizing Cotter's conclusions, McCord pointed out that the finding of positive cephalin-cholesterol flocculation reactions does not point to external chemical poisons as the cause of liver damage, as asserted by Cotter. In no case was there any proof adduced as to the causative importance of "thioglycolic acid" in producing the symptoms, other than temporal coincidence. In addition, one may question the validity of Cotter's report in that, since its publication in 1946, there have been no other reports of hepatic damage following cold waving, although usage of cold waves has since become nationwide.

Toxicity of neutralizer solutions has also been investigated. Sodium bromate was found lethal for rabbits by Santesson and Wickberg,[32] in oral dosage of 500 mg. per kilogram. In other studies, Humoller[33] found 8% mortality in experimental animals at a dosage level of 100 mg. per kilogram, 12% at 200 mg. per kilogram, increasing to 76% at 500 mg. per kilogram. Considerably lower toxicity levels were found in studies on perborate salts. Mulinos[34] reported 100% survival of experimental animals given perborate orally in dosage substantially exceeding the "human dose." Corresponding to the experimental findings on bromate toxicity, there have been reports of serious intoxication in children after accidental ingestion of bromide neutralizer solution.[35]

There were no recognized authentic cases of systemic intoxication following percutaneous application of waving agents in the series covered by this report.

OPHTHALMIC CHANGES

Mild irritation may be expected after accidental entry of thioglycolate or neutralizer solutions into the eye, particularly if the agent is not flushed out with water. Experimental studies in which thioglycolate and neutralizers were instilled in rabbit eyes showed mild transient conjunctival irritation, leaving no visible change in any instance after seven-day follow-up observation. No claims of ocular damage after accidental entry of waving solution into the eye were found in the representative period covered, other than occasional complaints of mild conjunctivitis when the solution was not flushed out of the eye with water as directed. In the entire file, covering some 70 million sales, there was one instance each of a complaint of optic neuritis and iridocyclitis. No explanation of the cause of the optic neuritis could be found after intensive investigation, and it was concluded that its development was coincidental. In the patient with iridocyclitis, acute ethmoid sinusitis was discovered on examination and was considered to be the causative factor.

CONCLUSIONS

1. Ammonium thioglycolate cold-wave formulations of the average concentration supplied for home use are below the threshold for primary irritation when used

32. Santesson, C. G., and Wickberg, G.: Ueber Wirkungen von Natriumbromat, Skandinav. Arch. Physiol. **30**:337-394, 1913.

33. Humoller, F.: Unpublished data.

34. Mulinos, M.: Unpublished data.

35. Neutralizers in Home Permanent Waving Kits, editorial, J. A. M. A. **144**:297 (Oct. 30) 1950.

according to directions, on normal skin. Misuse may result in irritation, in some instances, when gross failure to follow directions enhances the keratolytic potentiality of the active agent.

2. Ammonium thioglycolate has an exceptionally low sensitizing index; in general, where sensitization does develop it is of the eczematous-contact-dermatitis type.

3. Hair damage may occur in some instances in which the hair has been previously altered by dyes and bleaches, particularly when directions for use are not followed and over-long processing times are employed. Such damage is apparently limited to the hair shaft, and no inhibition of growth is observable.

4. Direct systemic toxic manifestations were not seen after percutaneous application of ammonium thioglycolate.

NATURAL STEROID COMPLEX

Evaluation of Use in Collagen Diseases and Chronic Dermatoses

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AND
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ANNOUNCEMENT of the dramatic effects of cortisone in the treatment of rheumatoid arthritis [1] and the promise of beneficial influence in the so-called collagen diseases [2] and conditions associated with allergy initiated the search for other compounds that might be equally effective without the undesirable side effects. This led to the production of "marisone," [3] a steroid complex of dry sterol conjugates that are separated from the estrogen conjugates present in the starting material. This product contains considerable amounts of the phenolic and neutral sterols derived from pregnant mare's urine and present as water-soluble conjugates. Study of the sterol conjugates shows that the ether-soluble fraction, after acid hydrolysis, has been partitioned into acidic, phenolic, and neutral fractions. The conjugates are present in the form of sulfates and glycuronides.

Jaros and Spielman,[4] in their study of the value of this product in bronchial asthma, found it to be safe, nontoxic, and well-tolerated in large doses. It exerted a profound effect in causing suppression of progressive pulmonary fibrosis, as indicated by marked increases in pulmonary vital capacities.

Because of encouraging beneficial results obtained with cortisone in certain dermatoses, the following study was conducted with "marisone" on patients exhibiting diffuse collagen diseases and on others with chronic dermatoses. The preparation was given without the patients' knowledge of the nature of the material, in a dosage of 200 mg. five times daily, and in a few instances the dose was doubled or tripled.

As indicated in the table 13 females and 9 males were included in this study, ranging in age from 14 to 72 years. In 14 the dosage was maintained throughout at 1,000 mg. daily, in 5 it was increased to 2,000 daily, and in 1 up to 3,000 daily, and in 2 it was decreased to 600 and 800 mg., respectively. The response was considered excellent in six, good in five, fair in three, and ineffective in eight. The diseases comprising this study included atopic dermatitis, psoriasis, pemphigus,

1. Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Effects of Cortisone Acetate and Pituitary ACTH on Rheumatoid Arthritis, Rheumatic Fever and Certain Other Conditions: A Study in Clinical Physiology, Arch. Int. Med. **85**:545-666 (April) 1950.

2. Thorn, G. W.; Forsham, P. H.; Frawley, T. F.; Hill, S. R., Jr.; Roche, M.; Staehelin, D., and Wilson, D. L.: Medical Progress: The Clinical Usefulness of ACTH and Cortisone, New England J. Med. **242**:824-833 (May 25) 1950.

3. "Marisone" was supplied by Ayerst, McKenna & Harrison, Ltd.

4. Jaros, S. H., and Spielman, A. D.: Natural Steroid Complex in the Treatment of Bronchial Asthma, Ann. Allergy **9**:308 (May-June) 1951.

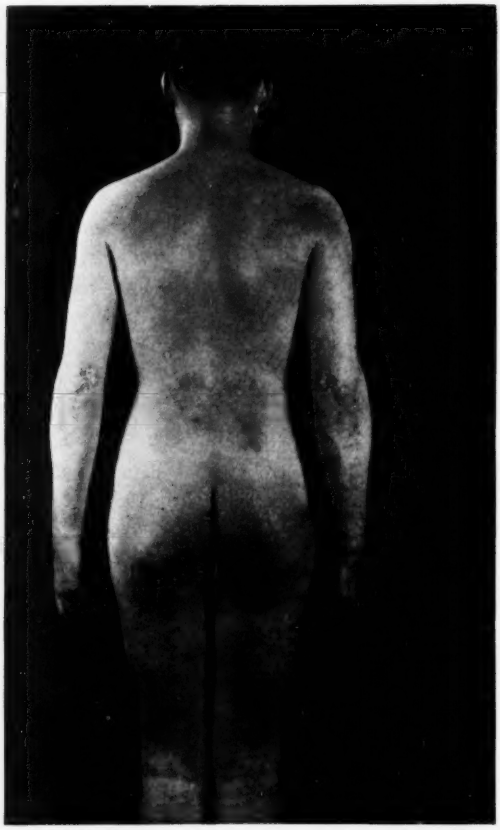

Fig. 1 (Case 18).—E. P., showing extent and distribution of eruption, Sept. 1, 1950.

Fig. 2 (Case 18).—E. P., showing lesions of palms and rheumatoid changes in fingers, Sept. 1, 1950.

Fig. 3 (Case 18).—E. P., showing only residual erythema or depigmentation in sites of previous lesions, Nov. 7, 1950.

Fig. 4 (Case 18).—E. P., showing palms entirely clear, Nov. 7, 1950.

neurodermatitis, keratoderma climactericum, urticaria, lupus erythematosus, dermatosis due to light sensitivity, seborrheic dermatitis, and contact dermatitis. Side effects were noted in six patients.

The patients in whom the response was recorded as excellent comprised two with pemphigus (Cases 3 and 10), two with contact dermatitis (Cases 9 and 12), and two with keratoderma climactericum (Cases 15 and 22). One patient each

Summary of Data on Patients Treated with "Marisone"

Case No.	Name	Age, Yr.	Sex	Diagnosis and Duration of Disease	Daily Dosage, Mg., and Duration of Treatment	Result	Side Effect
1	J. H.	22	F	Atopic dermatitis, 2 yr.	1,000-2,000, 2 mo.	Fair	None
2	S. R.	28	F	Atopic dermatitis, 1½ yr.	1,000, 3 mo.	Good	None
3	A. C.	50	F	Pemphigus, 7 mo.	1,000-600, 1½ mo.	Excellent	None
4	H. S.	34	F	Lupus erythematosus, 11 yr.	1,000-2,000, 6 wk.	No effect	None
5	H. S.	50	M	Atopic dermatitis, 8 yr.	1,000-2,000, 4 wk.	No effect	None
6	N. B.	14	F	Light sensitivity, 4 yr.	1,000, 4 wk.	Good	None
7	D. H.	17	M	Atopic dermatitis, 44 yr.	1,000, 4 wk.	Fair	None
8	E. K.	59	F	Atopic dermatitis, 33 yr.	1,000, 4 wk.	No effect	None
9	G. R.	58	M	Contact dermatitis, 1 yr.	1,000, 3 wk.	Excellent	None
10	M. V.	72	F	Pemphigus, 2½ yr.	1,000, 3 wk.	Excellent	Withdrawal bleeding
11	E. B.	46	M	Seborrheic dermatitis, eczematized, 3 mo.	1,000, 3 wk.	No effect	None
12	P. M.	46	F	Contact dermatitis, 17 days	1,000, 3 wk.	Excellent	None
13	F. K.	36	M	Neurodermatitis, 3 mo.	1,000, 1 wk.	No effect	None
14	L. C.	54	F	Neurodermatitis, 6 mo.	1,000, 3 wk.	Good	Enlargement of breasts
15	S. L.	47	F	Keratoderma climactericum, 1 yr.	1,000-600, 6 wk.	Excellent	Vaginal discharge with trace of blood; tenderness of breasts
16	B. H.	56	F	Psoriasis-Arthritis, 11 yr.	1,000, 3 wk.	No effect	Vaginal discharge and spotting on one occasion one week after drug stopped
17	C. E.	24	F	Urticaria, 2 days	2,000, 1 wk.	No effect	None
18	E. P.	35	M	Psoriasis-Arthritis, 10 yr.	1,000-2,000, 6 mo.	Good	Tenderness of nipples
19	B. B.	56	M	Psoriasis, 20 yr. Arthritis, 6 yr.	1,000-3,000, 3 mo.	Fair	Enlargement of breasts
20	S. B.	28	M	Urticaria, Angioneurotic edema, 6 mo.	1,000, 3 days	No effect	None
21	D. P.	48	M	Psoriasis, rhinitis, 15-20 yr.	1,000, 6 wk.	Good	None
22	G. H.	60	F	Keratoderma climactericum, 5 yr.	800-1,000, 6 wk.	Excellent	None

with atopic dermatitis (Case 2), dermatosis due to light sensitivity (Case 6), and neurodermatitis (Case 14) and two patients with psoriasis showed a good response (Cases 18 and 21). The response was only fair or entirely unsatisfactory in four patients with atopic dermatitis (Cases 1, 5, 7, and 8), in one each with chronic discoid lupus erythematosus (Case 4), neurodermatitis (Case 13), and seborrheic dermatitis (Case 11), and in two each with urticaria (Cases 17 and 20) and psoriasis (Cases 16 and 19).

Of the patients who showed an excellent response, the two with pemphigus were the most dramatic. The lesions progressed to complete healing in from one to three weeks, and both have remained free from lesions since the use of "marisone" was discontinued. In the two patients with keratoderma climactericum the response

was equally gratifying. Itching was controlled in a few days, the deep fissures began to heal, the thickening of the epidermis receded, and normal skin areas appeared within two weeks after therapy was started. These patients are still under treatment and observation, and they continue to show steady improvement. The two patients with contact dermatitis included one in whom the condition was of long standing, who had had many types of therapy and in whom a generalized eruption developed following a patch test with ragweed to which he was highly sensitized, and one patient with an acute condition, exhibiting edema, erythema, and vesiculation involving the head, neck, arms, and thighs. In both cases, the condition cleared completely, the more acute dermatitis in one week and the chronic condition in three weeks.

Psoriasis, which has responded to cortisone, has yielded only after prolonged treatment with "marisone" and has shown a tendency to relapse upon withdrawal of the drug. Case 18 showed improvement only after having taken the drug in a dosage of 2,000 mg. daily for almost a month. He regressed within 10 days after the use of the drug was discontinued, but he improved again when it was begun again. Case 21 showed steady improvement beginning with the 10th day of therapy but gradually regressed when the use of the drug was discontinued. In one patient with psoriasis (Case 16) there was no change after three weeks, while in another (Case 19) there was early improvement followed by regression in spite of increased doses of "marisone."

One patient with atopic dermatitis (Case 2) showed a good response to "marisone" after suffering a severe recurrence during pregnancy. The weeping and pruritus was controlled in 10 days, and she remained completely free from asthma. Four days after the drug was withdrawn she suffered a severe, generalized flare-up which was controlled with cortisone. In the other four patients with atopic dermatitis (Cases 1, 5, 7, and 8) the response was only fair to negligible.

In one patient with neurodermatitis (Case 13) there was no improvement, but the use of the drug was discontinued after one week, while the other patient with neurodermatitis showed good improvement after continuing the therapy for three weeks.

Two patients with urticaria (Cases 17 and 20) showed no response. In one (Case 17) the urticaria actually developed during "marisone" therapy for migraine.

The condition of the patient with solar sensitivity (Case 6) was completely controlled as long as she was under therapy but promptly relapsed when the use of the drug was discontinued.

One patient each with chronic discoid lupus erythematosus (Case 4) and seborrheic dermatitis which had become generalized and eczematized (Case 11) showed no response. The former received the drug in doses up to 2,000 mg. daily for four weeks, while the latter was unimproved after three weeks with a dosage of 1,000 mg. daily.

Side-effects were observed in six patients. In one this consisted of withdrawal bleeding, while in the others it consisted of enlargement and tenderness of the breasts, with associated vaginal discharge and spotting in two. In each instance these side-effects disappeared in a few days after use of the drug was discontinued or the dosage reduced. In both male patients side-effects were noted only after the drug had been taken for several months and in large doses, while in the female patients side-effects appeared after two or three weeks.

The most significant metabolic and biochemic effects were a drop in the number of white blood cells, which occurred after prolonged administration of the drug in a dosage which might, in retrospect, be considered as excessively high. In each instance that this occurred it coincided with tenderness of the nipples and tur-

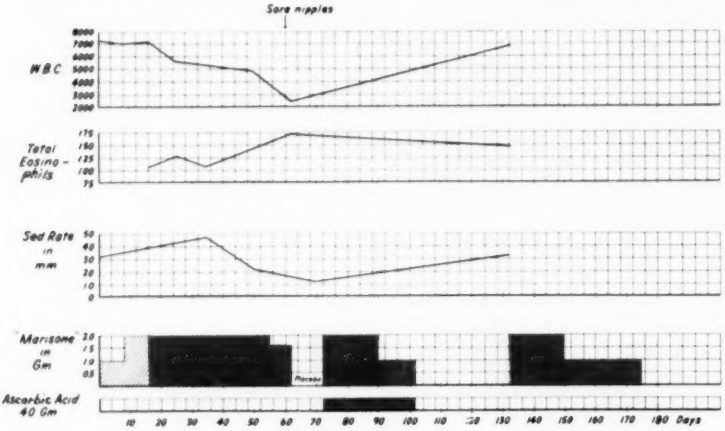
Sore nipples
W.B.C.
Total Eosino-phils
Sed Rate in mm
"Marisone" in Gm
Placebo
Ascorbic Acid 40 Gm
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 Days

Fig. 5 (Case 18).—Laboratory charts of E. P., psoriasis and arthritis. There was no effect on the red blood cell count, hemoglobin, platelets, uric acid, creatinine, blood sugar, urinary findings, or blood pressure.

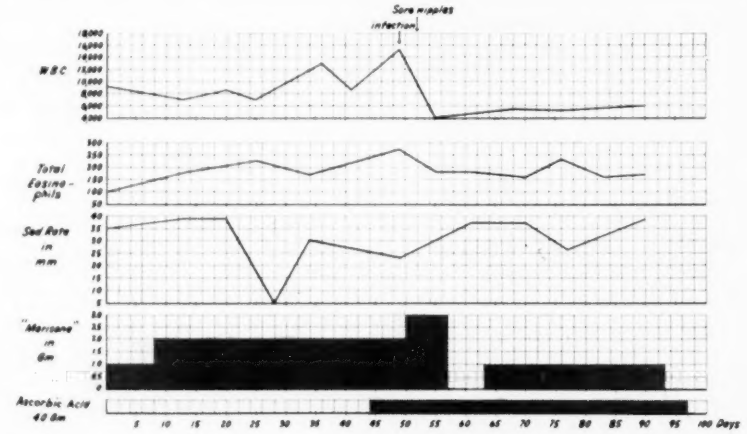
Sore nipples
infection
W.B.C.
Total Eosino-phils
Sed Rate in mm
"Marisone" in Gm
Ascorbic Acid 40 Gm
5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 Days

Fig. 6 (Case 19).—Laboratory charts of B. B., psoriasis and arthritis. There was no effect on the red blood cell count, hemoglobin, platelets, uric acid, creatinine, blood sugar, urinary findings, or blood pressure.

gescence of the breasts. This was noted in two male and two female patients. Millman and Maggio [5] also recorded this side-effect in three of their patients who received the drug in high dosages. In addition, one patient (aged 72) had a

5. Millman, M., and Maggio, G. E.: Treatment of Bronchial Asthma with a New Natural Steroid Complex, to be published.

typical menstrual period upon withdrawal of the drug, while two others, both postclimacteric, experienced vaginal discharge with bloody spotting. The hemoglobin and erythrocyte counts showed no significant change. Elevated sedimentation rates were reduced in relation to the improvement of the condition under treatment. The circulating eosinophiles showed some variation, which was considered insignificant. The blood pressure was apparently not affected by the drug. Excretion of 17-ketosteroids remained normal even after prolonged administration.

As indicated by the clinical evidence in this study, "marisone" appears to be helpful in certain dermatoses. The most striking results were obtained in two patients with pemphigus in whom all lesions healed completely in from one to three weeks. Equally responsive, but not as rapid were both keratoderma climactericum and contact dermatitis. In psoriasis with associated polyarthritis the response was gradual but definite, required more prolonged medication, and showed a tendency to relapse gradually when use of the drug was discontinued. It was ineffective in the patients who received the drug for less than one month. Atopic dermatitis and neurodermatitis also tended to show this same pattern. In its effect upon urticaria, as well as upon chronic discoid lupus erythematosus and seborrheic dermatitis, the drug must be listed as an absolute failure.

The side-effects of vaginal discharge, menstruation, and enlargement and tenderness of the breasts and nipples disappear after withdrawal of the drug.

SUMMARY

A study is presented of 22 patients exhibiting 10 dermatologic entities treated with "marisone," a natural steroid complex derived from pregnant mares' urine.

This complex is nontoxic and produced a minimum of side-effects even after prolonged administration with large doses.

Clinical experience indicates its beneficial influence in a variety of dermatoses, including pemphigus, contact dermatitis, and keratoderma climactericum.

The response was definite but characterized by relapse on withdrawal of the drug in psoriasis, neurodermatitis, atopic dermatitis, and light sensitivity.

In chronic discoid lupus erythematosus, seborrheic dermatitis, and urticaria, use of the complex in this study was a failure.

2561 First Ave. (3).

233 A St. (1).

BULLOUS ERUPTION DUE TO PEDICULOSIS PUBIS

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IN RECENT years some unusual cutaneous reactions produced by the head louse [1] and the body louse [2] have been described. It is the purpose of this paper to report a pemphigus-like eruption due to the third type, the pubic louse.

REPORT OF A CASE

A. P., a 79-year-old Italian man, was first seen in the dermatology clinic of Rhode Island Hospital on Sept. 11, 1950. He presented a vesicular and bullous dermatosis which was diagnosed as pemphigus vulgaris by the examining physician, and the patient was hospitalized two days later. A carefully taken history on admission disclosed that he had been well until about three weeks previously, at which time he noted several small blisters on the penis and scrotum. As these broke they were replaced by blood-red areas which gradually crusted and fell off. New blisters continued to appear about the inguinal regions and later on other parts. The face and back were spared. He had experienced no feverishness, chills, malaise, weight loss, or impairment of appetite, and itching had been mild. The examination, as recorded in the hospital chart, revealed clear, hemorrhagic, and purulent bullae, red and brown crusts, and brown pigmented areas on the neck, chest, upper extremities, penis, and lower extremities (Fig. 1). On the medial aspect of the right foot was a 3-by-4-cm. bulla filled with cloudy fluid. Mouth lesions were not present. The presence of pediculosis pubis was noted. Findings from the remainder of the physical examination were essentially normal except for a grade-2 apical systolic murmur and frequent ventricular extrasystoles. Laboratory values, including white blood cell count and differential cell count, fasting blood sugar, blood urea nitrogen, and results of urinalysis were normal, and reactions to serologic tests for syphilis were negative. The erythrocyte count and hemoglobin were low, the former being 2,820,000 per cubic millimeter and the latter 8.3 gm. per 100 cc. A biopsy specimen was taken on the day of admission and was interpreted by the general pathologist as "dermatitis, acute bullous; consistent with pemphigus."

During the period of hospitalization the patient's temperature was normal except for slight elevation in the first few days. Treatment consisted of 400,000 units of penicillin administered intramuscularly twice daily from Sept. 13 to Sept. 20, aureomycin in dosage of 0.5 gm. every six hours from Sept. 20 to Sept. 26, and potassium permanganate wet dressings to several areas. On the day of admission his skin was dusted with chlorophenothane ("D. D. T.") powder. By the eighth hospital day all bullae were gone except for some old crusted ones on the buttocks, arms, and thighs. During the next nine days only a few new lesions appeared, and on Sept. 30 he was discharged, 17 days after admission, with the diagnosis of pemphigus vulgaris and pediculosis pubis.

I saw the patient for the first time when he returned to the dermatology clinic on Oct. 16, 1950. He stated that lesions had recurred shortly after he had left the hospital. Itching was slight. Examination revealed a few discrete, hemorrhagic bullae on the wrists and crusted lesions

From the Department of Dermatology and Syphilology, Rhode Island Hospital, Dr. Francesco Ronchese, Chief of Service.

1. Ronchese, F.: Generalized Dermatitis from Pediculosis Capitis, New England J. Med. **234**:665 (May 16) 1946.

2. Morris, G. E.: Pediculosis Corporis and Leg Ulcers, New England J. Med. **233**:180 (Aug. 9) 1945.

on the wrists, thighs, and feet. Mouth lesions were absent and Nikolsky's sign could not be elicited. A great many nits were seen on the pubic, axillary, and chest hair; several adult crab lice were demonstrated in these regions. The eyelashes, eyebrows, and scalp hair were not involved. The course of the illness suggested that the dermatosis was not pemphigus but rather

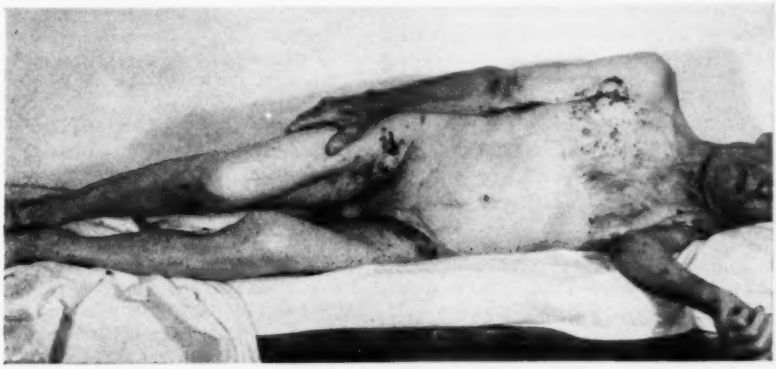

Fig 1.—Appearance of patient on Sept. 14, 1950, showing many hemorrhagic and crusted bullae. The arrow points to a large, clear bulla on the right thigh.

Fig. 2.—Low-power photomicrograph showing the highly projecting vesicle; hematoxylin and eosin.

the result of the Phthirus pubis infestation. Accordingly, the only treatment instituted was the local use of an aqueous emulsion of benzyl benzoate-chlorophenothane-ethyl aminobenzoate (topocide®). The patient did not return to the clinic until Nov. 3, 1950, at which time he reported that within four days of beginning this therapy all lesions had disappeared. Results of examina-

tion were essentially normal except for some small areas of pigmentation and the presence of a few nits on the axillary hair. He was advised to continue application of the benzyl benzoate-chlorophenothane lotion, and when seen one week later he was normal except for the previously noted pigmented spots. Subsequent attempts to induce him to return for reexamination were unsuccessful. However, on May 5, 1951, he stated in a telephone conversation that he had remained well and free of skin disease.

Dr. Fred D. Weidman kindly reviewed the biopsy section (Fig. 2), and his report was as follows: "The greater part of the section is occupied by this highly projecting vesicle. It must have had its beginning in the upper part of the corium, inasmuch as the epidermis has been lifted up bodily, leaving none of it attached to the floor of the vesicle. Moreover, at the one edge of the vesicle there is not the slightest trace of basement membrane, such as can be identified elsewhere. Most of the vesicle contents is a granular precipitate made up of serum albumin and globulin, together with a fibrin reticulum. Relatively few inflammatory cells are contained; what few there are, are concentrated at the bottom of the vesicle where the basement membrane is destroyed. There is only a narrow zone of edema under the vesicle; it contains a few fibroblasts. Incidentally, the epidermis is free from edema; it is normal, barring the compression of its cells which is the result of pressure from underneath. As to the interpretation, I am frank to say that I do not like the idea of pemphigus because the epidermis is not affected in the least. At the same time, I would object to dermatitis herpetiformis because the basement membrane has not been sufficiently disrupted, and for erythema multiforme there is not an adequate reaction in the corium. In short, histologically this does not agree with any of the three, and perhaps this is a point in favor of your thesis about the role of the pediculi. The reaction is not characteristic for allergy, unless it is of the purely edematous kind which is expressed in urticaria. Morphologically, in these sections I would diagnose a bullous urticaria, something like lichen urticatus, which, incidentally, has been regarded as the effect of flea bites."

COMMENT

Study of the "Quarterly Cumulative Index" and the "Quarterly Cumulative Index Medicus" from 1916 through March, 1951, disclosed no reports of bullous lesions associated with pediculosis pubis. Nuttall [3] did considerable work on the subject of pediculosis and in 1917, 1918, and 1919 published several excellent reviews, including a bibliography of 639 articles. In his discussion of the pathologic effects of Phthirus pubis,[3d] there was no mention of its producing bullae.

On the basis of the clinical and histopathologic evidence, however, it appears to be most probable that the dermatosis in the case being reported was due to the crab louse. Pemphigus, dermatitis herpetiformis, erythema multiforme, and other bullous eruptions can be excluded by the absence of constitutional symptoms, denial of using drugs, minimal pruritus, distribution of lesions, and prompt response on two occasions to pediculocidal therapy.

As described in the literature, the cutaneous effects of Phthirus pubis are twofold: the pale bluish-gray maculae and pruritus. The latter varies in degree, some persons harboring the organism for years with no symptoms whatsoever, and others experiencing extremely severe itching. As a result of the scratching, excori-

3. Nuttall, G. H. F.: (*a*) Bibliography of Pediculus and Phthirus, Including Zoological and Medical Publications Dealing with Human Lice, Their Anatomy, Biology, Relation to Disease, etc., and Prophylactic Measures Directed Against Them, Parasitology **10**:1 (Nov.) 1917; (*b*) The Part Played by Pediculus Humanus in the Causation of Disease, ibid. **10**:43 (Nov.) 1917; (*c*) The Biology of Pediculus Humanus, ibid. **10**:80 (Nov.) 1917; (*d*) The Pathological Effects of Phthirus Pubis, ibid. **10**:375 (April) 1918; (*e*) The Biology of Phthirus Pubis, ibid. **10**:383 (April) 1918; (*f*) Combating Lousiness Among Soldiers and Civilians, ibid. **10**:411 (May) 1918; (*g*) The Biology of Pediculus Humanus, ibid. **11**:201 (Feb.) 1919; (*h*) The Systematic Position, Synonymy and Iconography of Pediculus Humanus and Phthirus Pubis, ibid. **11**:329 (Oct.) 1919.

ations, pigmentation, papules, and eczematization may be produced. Nuttall [3d] described the case of a soldier with heavy infestation by Phthirus pubis in whom severe eczematous inflammation of both axillae developed where hundreds of lice were found, the dermatitis being due to the continual scratching. He also cited cases of papular eruptions with eczematous inflammation reported by Morris and by Dubreuilh and Beille. In all these instances the cutaneous change was the result of scratching.

The patients herein described presented a discrete, bullous rather than eczematous reaction, and, furthermore, the pruritus was minimal. Accordingly, the bullae must have been due to the bite of the louse per se and/or to a toxin or antigen resulting from the bite and carried via the blood or lymphatics to distant points. The problem raised is perhaps analogous to that concerning papular urticaria and flea bites. Blank and his co-workers [4] have recently reemphasized the role of the insect, particularly the flea and bedbug, in the production of this dermatosis. They obtained a high incidence of cure in a series of patients with papular urticaria with therapy limited to use of a 5% chlorophenothane dusting powder and chlorophenothane household spray. Skin tests indicated that many of these patients are abnormally sensitive to these insects. Smith [5] has stated in regard to the effect of fleas,

> In addition to typical bites one occasionally sees scattered urticarial papules which do not appear to be the result of bites and presumably are an allergic response to absorption of toxin from the bitten areas.

Lunsford [6] pointed out that in papular urticaria many of the papules are allergic reactions to one or a few bites and are a manifestation of sensitivity to the antigen injected by the bite of the flea. He also noted that a generalized, erythema-multiforme-like, bullous eruption may occasionally be associated with flea infestation.

Payne,[7] in 1890, described the case of a 16-year-old boy with severe headache, fever, nausea and giddiness, and pediculosis pubis. Removal of the pediculi was followed by prompt disappearance of his symptoms. Payne suggested that the constitutional symptoms might be due to poisoning from a chemical substance introduced by the bite of the louse. Nuttall [3d] stated,

> Apart from the maculae, Phthirus, like P. humanus, fleas, and mosquitoes, may cause a febrile condition owing to skin irritation, although this appears to be rare; with removal of the lice, the fever promptly subsides.

Safdi and Farrington [8] reported the cases of two patients with fever and moderately

4. Shaffer, B.; Spencer, M. C., and Blank, H.: Papular Urticaria: Its Response to Treatment with DDT and Role of Insect Bites in Its Etiology, J. Invest. Dermat. **11**:293 (Oct.) 1948. Blank, H.; Shaffer, B.; Spencer, M. C., and Marsh, W. C.: Papular Urticaria: Study of the Role of Insects in Its Etiology and the Use of DDT in Its Treatment, Pediatrics **3**:408 (March) 1950.

5. Smith, L. M., in discussion on Lunsford, C. J.: Flea Problem in California, Arch. Dermat. & Syph. **60**:1184 (Dec.) 1949.

6. Lunsford, C. J.: Flea Problem in California, Arch. Dermat. & Syph. **60**:1184 (Dec.) 1949.

7. Payne, J. F.: Maculæ Cæruleæ and Other Symptoms Produced by Pediculi Pubis, Brit. J. Dermat. **2**:209, 1890.

8. Safdi, S. A., and Farrington, J.: Constitutional Reactions and Maculæ Ceruleæ Attending Phthiriasis Pubis, Am. J. M. Sc. **214**:308 (Sept.) 1947.

severe constitutional symptoms associated with massive infestation of pubic lice who made a rapid and complete recovery on removal of the parasites.

Tièche [9] observed experimentally that the bite of Phthirus pubis produced a brown spot which became bluish after eight hours. Nuttall [3d] was unable to find any other record in the literature concerning the experimental feeding of this organism. He conducted two experiments himself. In the first, he allowed an adult crab louse to feed on one small area of his arm for 25 hours, at the end of which time it was removed and the site of the bite marked. A small, faint, deep-seated violet spot was noted, and this disappeared in one week. In the second, freshly emerged larvae were placed on the skin. After four days of feeding in one area, a faint pink color was observed. As the larvae reached the adult stage the effects of further bites became somewhat more marked. In no instance were bullae produced.

A review of the subsequent literature failed to disclose any articles on similar experimental studies. However, there have been corresponding investigations with Pediculus corporis. Moore [10] reported the occurrence of general malaise, headache, chills, and fever after his feeding of this parasite. He also reported the development of a morbilliform eruption, while in another subject a number of small blisters developed on the arm where the lice were fed, as well as a macular rash over the neck and shoulders. Hirschfelder and Moore [11] allowed four subjects to be bitten, and in three a macular eruption appeared on areas distant to the site of feeding, and in three there was a rise in temperature. Although not an experimental study, the observation of Milian [12] might be mentioned at this time. He described an unusual manifestation of pediculosis corporis consisting of papulovesicles which he believed were not the immediate result of a bite but rather the effect of an auto-intoxication due to the bites in other parts. Peck and his co-workers,[13] as a result of their investigations, concluded that there are two phases in the skin reaction following exposure to the body louse. The first is the purpuric reaction due to the introduction of the proboscis and the act of feeding. The second is the inflammatory phase which is due to hypersensitivity developed after repeated exposures. When large numbers of lice were fed on a very sensitive person, vesiculation was observed in the feeding area. Correspondingly, they noted the greatest skin reaction to intradermal injection of antigens prepared from louse heads and feces in those persons who exhibited the most marked reaction after exposure to the lice. In one of their subjects who had had Phthirus pubis infestation five years previously, a vesicular reaction developed after the first exposure to only 50 body lice. It was their belief that this man was hypersensitive and that this might have been due to cross sensitization of his previous infestation with Phthirus pubis.

SUMMARY AND CONCLUSIONS

The case of a patient with a bullous eruption, originally diagnosed as pemphigus vulgaris, associated with pediculosis pubis, is reported. The clinical and histo-

9. Tièche, cited by Nuttall.[3d]

10. Moore, W.: An Interesting Reaction to Louse Bites, J. A. M. A. **71**:1481 (Nov. 2) 1918.

11. Hirschfelder, A. D., and Moore, W.: Clinical Studies on the Effects of Louse Bites: Pediculus Corporis, Arch. Int. Med. **23**:419 (April) 1919.

12. Milian, G.: La phtiriase aigue, Médecine **3**:138, 1921-1922.

13. Peck, S.M.; Wright, W.W., and Gant, J. Q., Jr.: Cutaneous Reactions Due to the Body Louse (Pediculus Humanus), J. A. M. A. **123**:821 (Nov. 27) 1943.

pathologic evidence suggests that the dermatosis was not pemphigus, but rather the result of the infestation.

The decision as to whether the lesions were the result of the louse bite per se or a reaction to an antigen introduced by the bite is more difficult to make. When first seen, as shown in Figure 1, the bullae were predominantly about the axillae and inguinal areas, suggesting that they might have been the direct result of bites. However, at the time of recurrence the lesions were present on the wrists and lower extremities, with sparing of the axillae and inguinal regions. It is difficult to believe, although the possibility nevertheless exists, that each of the multiple bullae was itself the site of a louse bite. The pathologic picture observed microscopically pointed away from this and suggested a reaction similar to the papular urticaria response to the flea bite. The experimental studies of Tièche [9] and Nuttall [3d] failed to demonstrate bulla formation, while the observations of Payne,[7] Nuttall,[3d] and Safdi and Farrington [8] indicated that some toxin or antigen was introduced into the blood stream as a result of crab-louse infestation. The investigations of Peck and his co-workers [13] demonstrated that a vesicular reaction may follow the bites of a body louse in the case of a hypersensitive subject. It is possible that similar studies with the pubic louse might yield the same results. Accordingly, it appears likely that the bullous eruption in the case being reported was the allergic reaction of a hypersensitive person to an antigen introduced by the bite of Phthirus pubis.

247 Waterman St. (6)

Dr. Fred D. Weidman examined the microscopic sections and made suggestions on the preparation of the paper. The photographs were taken by Burton C. Staugaard.

SYRINGOCYSTADENOMA PAPILLIFERUM AND NEVUS SEBACEUS (JADASSOHN) OCCURRING AS A SINGLE TUMOR

Report of a Case

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SYRINGOCYSTADENOMA papilliferum with nevus sebaceus combined in one lesion as a mixed tumor is interesting, not alone for its comparative rarity, but because its occurrence in the past has been the basis for the belief that these two histologically distinct structures are thereby histogenetically related and that their presence is the end-result of a dysontogenesis.

Regarding the essential cellular make-up of syringocystadenoma papilliferum, opinion is far from unanimous. Almost all the reports of this relatively rare tumor have described it as of sweat-gland origin, with the definite inference that the sweat glands involved were of the eccrine type. This was based on the supposed presence of eccrine-type glands both in the matrix of the lesion itself and in the immediately adjacent areas. Thus, Arzt and Kumer,[1] in the first description of combined syringocystadenoma papilliferum and nevus sebaceus (1925), referred to the glands as greatly dilated sweat glands, with no distinction as to whether they were eccrine or apocrine. Schiefferdecker's [2] biological observations on the sweat glands and his differentiation of them into eccrine and apocrine glands appeared at about the same time, and it is quite probable that his work was, dermatologically, unknown. However, Arzt and Fuhs in their later text on sweat gland nevi,[3] in which they included the original woodcuts of pathologic sections of the first described case of combined syringocystadenoma papilliferum and nevus sebaceus,[1] referred again to the glands in question as "greatly dilated sweat glands." That these authors by this time considered them eccrine is evidenced by the fact that, in their chapter on nevus sebaceus,[4] seemingly morphologically similar glands are definitely designated as apocrine. Similarly, in the first presentation of cases of nevus sebaceus in the

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Arzt, L., and Kumer, L.: Über Drüsennävi, Arch. Dermat. u. Syph. **148**:323, 1925.

2. Schiefferdecker, P.: Die Hautdrüsen des Menschen und der Säugetiere, ihre biologische und rassenanatomische Bedeutung, sowie die Muscularis sexualis, Biolog. Zentralbl. **37**:534, 1917; also Stuttgart, E. Scheizerbert, 1922.

3. Arzt, L., and Fuhs, H., in Arzt, L., and Zieler, K.: Die Haut- und Geschlechtskrankheiten, Berlin, Urban & Schwarzenberg, 1935, Vol. 2, p. 1094.

4. Arzt and Fuhs,[3] p. 1108.

American dermatological literature, Robinson[5] reported the diagnosis in two as nevus sebaceus and apocrine glands; all four cases were observed in Arzt's clinic.

On the basis of the present report, the thesis is presented that syringocystadenoma papilliferum is basically apocrine, that the glands present in its matrix and in close proximity to it are nevoid and apocrine and essentially the same as those that may accompany a sebaceus nevus. The latter assumption has been emphasized by Koch.[6] I further believe that, as stated by Lever,[7] the concurrent presence of nevus sebaceus and syringocystadenoma papilliferum is indicative of an embryological relationship between the two, and that the two have a similar primordial origin, the primary epithelial germ, which gives rise to apocrine and sebaceous glands but not to eccrine sweat glands.

It is recognized that apocrine glands are not normally present in the scalp, where the lesion described in this report was located. However, ontogenetically, an aberrant apocrine structure may be found in any location in which hair is present or in which hair is destined to appear. As a result of dysembryogenesis, a syringocystadenoma papilliferum could very well appear in the area in which it was found in this instance.

REPORT OF CASE

A 19-year-old youth was seen in 1949 for a scalp growth which he stated had been present since early childhood. It had always been irritated by combing and for many months had been rather tender. During this period it had "broken down" and had discharged a seropurulent fluid.

Examination revealed a tumor on the scalp vertex measuring 4 by 1.5 cm. Its surface was uneven and presented numerous projecting hairs. Plaque-like, it consisted almost entirely of closely aggregated, grayish, pin-head-sized, moist nodules.

Histologic Examination.—A tumor mass was present in the upper portion of the corium, occupying one half of the section. The epidermis on both sides of the mass evidenced hyperkeratosis and acanthosis. When the epidermis was followed to the area of the tumor, there was noted an invagination of the surface epithelium with the formation of projecting villus-like structures into a cystic space. Beneath the villi were various-sized apocrine glands. The nuclei of their lining cells were hyperchromatic and their cytoplasm acidophilic. Some of the glands presented definite evidence of active secretion with droplets of acidophilic cytoplasm extruding into their lumens. Collections of clumped, decapitated cells were visible in the latter. Other glands, in a resting stage, showed lumens entirely or partially filled with acidophilic and homogeneous cytoplasm. The villi were lined by a double layer of cells, an outer small cuboidal layer with round, basally placed nuclei and an inner high cylindrical layer with elongated, oval-shaped nuclei showing subnuclear vacuolation, the latter probably representing active secretion. The cells of the villi stained acidophilic.

The stroma of the villi contained many small capillaries and was heavily infiltrated with plasma cells. An occasional mitotic figure was present. The corium underlying the tumor was similarly infiltrated with plasma cells.

The other half of the section presented a hyperkeratotic and acanthotic epidermis, with many large sebaceous glands immediately below it and occupying almost the entire corium. In some places the epidermis invaginated downward and seemingly enclosed groups of sebaceous gland; in other portions, sebaceous glands appeared as though connected with the basal layer.

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5. Robinson, S. S.: Naevus Sebaceus (Jadassohn), Arch. Dermat. & Syph. **26**:663 (Oct.) 1932.

6. Koch, F.: Über Vorkommen von apokrinen Drüsen in Talgdrüsennaevi, Arch. Dermat. u. Syph. **174**:126, 1936.

7. Lever, W. F.: Pathogenesis of Benign Tumors of Cutaneous Appendages and of Basal Cell Epithelioma, Arch. Dermat. & Syph. **57**:679 (April) 1948.

HISTORICAL ASPECTS AND LITERATURE

Both nevus sebaceus and syringocystadenoma papilliferum have been designated by Arzt and Kumer [1] as nevoid tumors, hamartomatous in character. Since Jadassohn's [8] first description of nevus sebaceus, and his separation of it from adenoma sebaceum of Pringle and of Balzer and Hallopeau, very little has appeared in the American literature regarding this entity. Downing [9] and Maloney [10] presented several cases before dermatological societies. The four cases reported by Robinson [6] were, however, studied in Arzt's Vienna clinic. In Europe, where its

Fig. 1.—Syringocystadenoma papilliferum and nevus sebaceus. Invagination of epithelium with formation of projecting villus-like structures into cystic spaces is evident. Large apocrine glands staining eosinophilic are in and below the syringocystadenoma papilliferum portion of the tumor. The nevus sebaceus portion of the tumor shows many large groups of sebaceous glands immediately below the epidermis. They extend deeply and almost entirely replace the corium.

8. Jadassohn, J.: Bemerkungen zur Histologie der systematisierten Naevi und über Talgdrüsen-Naevi, Arch. Dermat. u. Syph. **33**:355, 1895.

9. Downing, J. G.: Localized Group of Enlarged Sebaceous Glands, Arch. Dermat. & Syph. **23**:790 (April) 1931.

10. Maloney, E. R.: Nevus Sebaceus Linearis, Arch. Dermat. & Syph. **30**:167 (July) 1934.

occurrence was considered pathogenetically significant because of its not infrequent combination with other structures, such as apocrine glands, syringocystadenoma papilliferum, and epithelioma, some 40 cases had, according to Savatard,[11] been described up to 1941. A most recent example was that by Prakken,[12] in which nevus sebaceus and benign cystic epithelioma were concurrently present. That nevus sebaceus may occur in this country more frequently than the paucity of American reports indicates, however, is evidenced by the illustrations of unreported

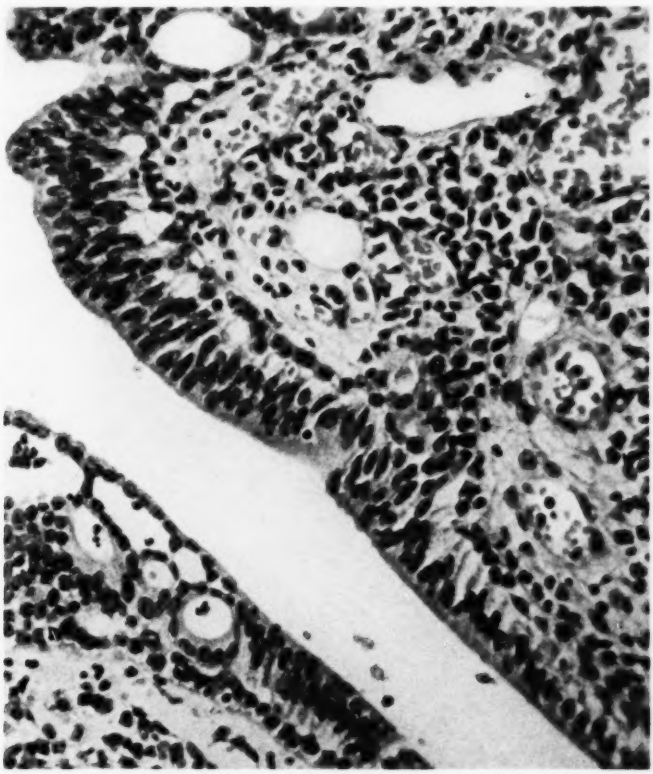

Fig. 2.—Villus showing two layers of cells, an outer cuboidal layer with hyperchromatic, basally placed nuclei and an inner columnar layer showing submuclear vacuolation probably representing active secretory activity. In their morphology and acidophilic staining they resemble apocrine duct cells. The stroma of the villus is heavily infiltrated with plasma cells.

cases of nevus sebaceus, by itself and in combination with basal-cell epithelioma by Montgomery [13] and Lever [7] in their respective works on the histogenesis of basal-cell epithelioma.

11. Savatard, L.: Naevus Sebaceus and Sebaceous Carcinoma, Brit. J. Dermat. **53**:214, 1941.

12. Prakken, J. R.: Syringo-Steato-Adenoma papilliferum cysticum vulvae, Acta dermat.-venereol. **27**:432, 1947.

13. Montgomery, H.: Histogenesis of Basal-Cell Epithelioma, Radiology **25**:8 (July) 1935.

Syringocystadenoma papilliferum is also comparatively rare. Beerman [14] recently stated that he had encountered only one example among 3,000 specimens for biopsy taken from cutaneous lesions and submitted to his laboratory for examination. Since its first description in the American literature by Stokes,[15] a total of 15 cases have been either reported or mentioned. Six of these, including the case in this report, presented added histological elements characteristic or strongly suggestive of nevus sebaceus. Concerning the six cases of syringocystadenoma papilliferum to which he referred, Lever [7] stated that excess amounts of mature or

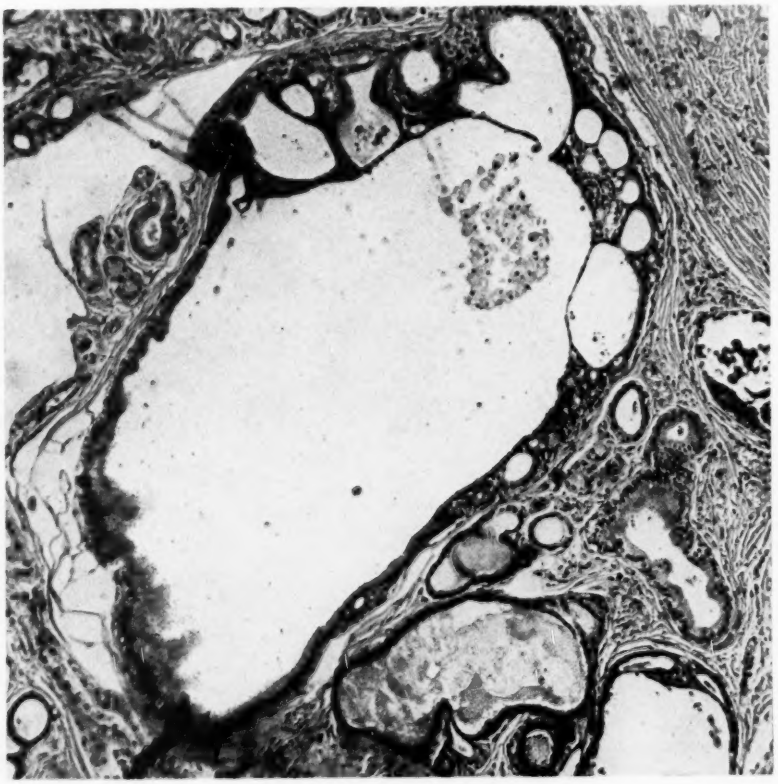

Fig. 3.—Large apocrine gland in the matrix of syringocystadenoma papilliferum. Active decapitation secretion is evident in this and in neighboring glands. Several glands are in a resting stage and either entirely or partially filled with cytoplasm. Clumps of decapitated acidophilic cells are present in the lumen of the large gland.

nearly mature sebaceous glands were within the tumor in four instances; hence the impression was gained that these tumors represented a combination of syringocyst-

14. Beerman, H.: Hypertrophic Darier's Disease and Nevus Syringocystadenomatosus Papilliferus: Histopathologic Study, Arch. Dermat. & Syph. **60**:500 (Oct.) 1949.

15. Stokes, J. H.: A Clinico-Pathologic Study of an Unusual Cutaneous Neoplasm Combining Syringadenomatosus Papilliferus and a Granuloma, J. Cutan. Dis. **35**:411 (Aug.) 1917.

adenoma papilliferum and nevus sebaceus. The recent case by Marcus and Woolridge [16] was one of syringocystadenoma papilliferum and nevus sebaceus.

In 1925 Arzt and Kumer [1] described three nevoid scalp tumors present since birth. In one, syringocystadenoma papilliferum was present by itself; in the other two it was combined with nevus sebaceus. The authors suggested the designation "naevus syringocystadenomatosus papilliferus et sebaceous" for the last two cases.

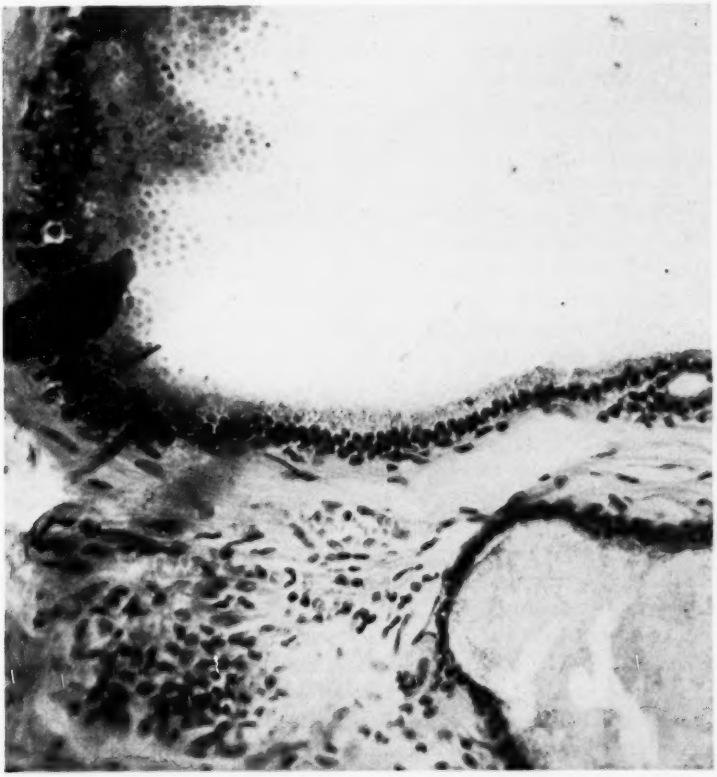

Fig. 4.—Portion of a large apocrine gland (at the left) showing the characteristic decapitation secretion in which droplets of acidophilic cytoplasm are extruded from the lining cells into the apocrine-gland lumen.

Dörffel,[17] in 1934, cited an instance in which a tumor diagnosed as syringocystadenoma papilliferum was removed and then recurred six months later at the site

16. Marcus, M. D., and Woolridge, W. E.: Sebaceous Nevus and Nevus Syringoadenomatosus Papilliferus Occurring as a Mixed Form: Report of a Case, Arch. Dermat. & Syph. **61**:105 (Jan.) 1950.

17. (*a*) Dörffel, J.: Naevus syringo-cystadenomatosus papilliferus, Dermat. Wchnschr. **99**: 1318 (Oct. 13) 1934; (*b*) Zur Histogenese des Naevus syringo-cystadenomatosus papilliferus, ibid. **100**:229 (Feb. 23) 1935.

of excision as nevus sebaceus. Shortly thereafter, Dörffel [18] reported a case of a scalp tumor which showed, histologically, combined syringocystadenoma papilliferum, nevus sebaceus, and epithelioma. He applied the diagnostic name of "syringocystadenomatosus papilliferus et sebaceous et epitheliomatosus" to it.

COMMENT

By themselves syringocystadenoma papilliferum and nevus sebaceus may, perhaps, be considered only interesting histological rarities. Their not uncommon combined presence as one tumor is, I believe, significant and important in connection with the possibly correct appraisal of their pathogenesis. Embryogenetically, their concurrent presence indicates a probable common anlage. Thus, Arzt and Kumer,[1] in discussing their cases, stated that the presence of syringocystadenoma papilliferum and nevus sebaceus in one case, and additional rudimentary hair growths in another, indicated a common origin for all three histologically distinct structures, namely, the primary epithelial germ. Dörffel expressed an essentially similar opinion.[19] However, there is one discrepancy in their analyses, and that is their designation of syringocystadenoma papilliferum as a sweat-gland tumor with the implication, therefore, that it is eccrine. This conception has obtained up to quite recently. Beerman,[14] in the past year, for example, stated that the essential pathologic picture of syringocystadenoma papilliferum is an involvement of the sweat glands and ducts, that it bears no relation to the pilosebaceous appendages, and that the apocrine apparatus is not involved. There have been exceptions, however, to this interpretation of its probable pathogenesis.

Beck [20] was of the opinion that syringocystadenoma papilliferum was apocrine in origin because its visible glandular lumens occasionally lead into hair follicles and because it is frequently accompanied by excessive amounts of sebaceous glands. Lever [7] has presented photomicrographic proof of the former occurrence. Also, Foot,[21] in the caption of an illustration of "papillary cystic hydradenoma," the name he applies to syringocystadenoma papilliferum in his text, states that it represents an overgrowth of sudoriparous ducts of apocrine glands. Morphologically, the histopathologic findings of the case in the present report permit a similar conclusion.

The conception of syringocystadenoma papilliferum as a nevoid tumor with an essential apocrine rather than eccrine make-up is necessary, if it is to coincide with the expressed opinions that its anlage is the primary epithelial germ. In his study of tumors of the cutaneous appendages, in which category he placed nevus sebaceus and syringocystadenoma papilliferum, Lever [7] stated that epidermal-appendage tumors are primary epithelial-germ tumors because of their origin from the primary epithelial germ, the anlage for hair and sebaceous and apocrine glands. He believes that the primary epithelial germ may attain a certain degree of differentiation toward the appendage it is originally destined to form later, when, as a result of dysembryogenesis, the ensuing growth will display either sebaceous, apocrine, or

18. Dörffel, J.: Zur Histogenese des Naevus syringo-cystadenomatosus papilliferus, Dermat. Wchnschr. **101**:855 (July 13) 1935.

19. Dörffel,[17b] Dörffel,[18]

20. Beck, S. C.: Syringoma, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, vol. 12 (Pt. 2) p. 458.

21. Foot, N. C.: Identification of Tumors, ed. 1, Philadelphia, J. B. Lippincott Company, 1948, pp. 334-335.

hairlike characteristics. On this basis, nevus sebaceus is classified as an organic sebaceous hamartoma because of its complete or almost complete differentiation toward the sebaceous gland; syringocystadenoma papilliferum is classified as an organoid apocrine-duct adenoma (hamartoma) because its essential cells, though not as well-differentiated as in nevus sebaceus, present suggestive apocrine duct cell morphology. Way and Memmesheimer,[22] much earlier, called attention to the primary epithelial-germ origin of the cutaneous appendages and emphasized that in the embryological development of the skin they were the first forms to differentiate and separate. They contrasted the cutaneous appendages with the eccrine sweat gland, which they stated had its origin in undifferentiated epithelium and appeared later. Hypothetically, it may be assumed, therefore, that with the onset of neoplasia the primordial antecedent of a sweat gland (eccrine) might develop into an undifferentiated structure, diagnostically indistinguishable.

Koch [6] reported a case of a nevoid growth on the cheek which, on histological examination, showed a nevus sebaceus and immediately below it many tubular glands with definite apocrine characteristics. The nuclei of their lining cells were hyperchromatic; their cytoplasm was acidophilic and in process of decapitation, with clumped cells in the gland lumens. This author stated that the presence of apocrine glands in an area where they are not usually found indicated that they were nevoid. That both sebaceous and apocrine glands have a common anlage emphasized the impression that in his case the nevus sebaceus and the nevoid apocrine glands were expressions indicating dysembryogenesis of their primary epithelial germs.

SUMMARY

A case presenting the typical histopathologic picture of both syringocystadenoma papilliferum and nevus sebaceus is reported. The syringocystadenoma papilliferum portion of the tumor showed the typical findings of apocrine glands and ducts. This would seem to indicate that this growth is an apocrine hamartoma. Usually present since birth or early childhood and not uncommonly accompanied by nevus sebaceus, its occurrence together with nevus sebaceus may be explained by a dysembryogenetic involvement of their anlage, the primary epithelial germ.

18 Willard Rd. (46).

Bruno E. Mickeleit, clinical photographer of the West Roxbury Veterans Administration Hospital, aided in this study.

22. Way, S. C., and Memmesheimer, A.: The Sudoriparous Glands: I. The Eccrine Glands, Arch. Dermat. & Syph. **34**:797 (Nov.) 1936; II. The Apocrine Glands, ibid. **38**:373 (Sept.) 1938.

EFFECT OF CORTISONE UPON HYPERSENSITIVITY DUE TO LYMPHOGRANULOMA VENEREUM

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AND
ROBERT J. WYSE, M.D.
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THE FREI intradermal reaction used for the diagnosis of lymphogranuloma venereum is, like the tuberculin reaction, a manifestation of delayed-type hypersensitivity. The former reaction is regarded as positive when the test site presents at the end of 48 or 72 hours a papule or indurated area which measures not less than 6 mm. in diameter. Erythematous zones may or may not surround the papule or indurated area, and the size of such zones is a much less reliable measure of the intensity of the reaction than the size of the papule or indurated area. The microscopic architecture of the Frei reaction is not diagnostic of lymphogranuloma venereum. Complement-fixing antibodies appear in the blood serum of lymphogranulomatous persons and can be detected and measured by the use of an antigen identical with that employed in the intradermal test, namely, an inactivated suspension of the virus agent of this disease. The present study was undertaken to determine the effect of cortisone upon the Frei intradermal reaction, upon the titer of complement-fixing lymphogranuloma reagin in the blood serum, and upon the histologic picture of the Frei-test site.

MATERIALS AND METHODS

Cortisone was injected intramuscularly into a lymphogranulomatous subject in a dose of 100 mg. twice daily for six days and on the succeeding two days in doses of 50 and 25 mg., respectively. Frei intradermal reactions were performed 11 days before cortisone treatment, on the 4th day of treatment, and on the 9th day after completion of treatment. The size of the reaction was measured at 48, 72, and 96 hours after the performance of the test; the result shown in the table is the 72-hour reading, which, in all instances, differed only insignificantly from the earlier and later readings. The complement-fixing titer of the blood serum was determined before, during, and after completion of cortisone treatment. Portions of the areas of reaction to the Frei intradermal tests performed before and during cortisone treatment were removed for histologic examination.

RESULTS

The size of the Frei reaction and the titer of the complement-fixing antibodies of the blood serum are shown in the table. A strongly positive reaction before cortisone

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treatment was replaced by a negative reaction during treatment; six days after administration of the drug was terminated the reaction was again positive. The complement-fixing titer of the blood serum was unchanged by the treatment. The biopsy specimen taken before cortisone treatment showed a normal epidermis with a large vesicle separating the basal-epidermal layer from the corium. The vesicle fluid contained few cells, of which lymphocytes were the most abundant. The blood vessels of the upper portion of the corium were dilated and engorged. Hemorrhage in the form of single or small clumps of erythrocytes was present throughout the corium which was also edematous. Some lymphatics were well filled with macrophages and lymphocytes together with a small number of polymorphonuclear leucocytes. All the blood vessels were surrounded by a well-delimited infiltrate of lymphocytes, with some polymorphonuclear leucocytes. In the upper portion of the corium, bordering upon the vesicular area, the infiltrate appeared as a narrow band parallel to the surface of the skin. In the lower portion, however, the infiltrate was more massive and discontinuous. Scattered throughout the corium, more particularly in the deeper

Effect of Cortisone upon Frei Intradermal Reaction and Complement-Fixing Titer of Blood Serum in Lymphogranuloma Venereum

Date	Cortisone, Mg./Day	Frei Reaction, Size of Papule	Complement-Fixing Titer of Blood Serum
Jan. 10, 1951	...	45 by 42 mm., with central vesicle 12 by 4 mm.	.....
Jan. 16, 1951	...	.....	1 in 40
Jan. 19, 1951 through Jan. 23, 1951	200	.....	.....
Jan. 24, 1951	200	No reaction	1 in 40
Jan. 25, 1951	100	.....	.....
Jan. 26, 1951	50	.....	1 in 40
Feb. 4, 1951	...	8 by 7 mm.	1 in 40

layers, were a moderate number of eosinophiles occurring either singly or in pairs. They were most commonly found just beyond the outermost limit of the perivascular infiltrate. The biopsy specimen taken during cortisone treatment showed no abnormal features except a narrow zone of lymphocytes and sparse polymorphonuclear leucocytes around a few blood vessels. Eosinophiles were not seen.

COMMENT

Circulating antibody was present and able to unite with an antigen in a demonstrable fashion and in equal concentration before and during cortisone treatment. The same antigen during cortisone therapy was unable to evoke a response of any of the tissue elements which constitute the specific skin reaction demonstrable before and after treatment. It would then follow that all of the elements of the tissue response were the product of an antigen-antibody reaction, with the exception of a small proportion of the perivascular zone of lymphocytes which probably arises from the introduction of foreign protein into the corium. No explanation can be offered of the effect of cortisone upon the development of tissue antibodies to the agent of lymphogranuloma venereum, or upon their ability to unite with specific antigen, or of the difference in action of the drug upon the circulating and tissue antibodies.

SUMMARY

In a person with lymphogranuloma venereum there was a strongly positive Frei reaction before administration of cortisone. While the patient was being treated with cortisone, this reaction appeared inhibited, but it was again positive after discontinuance of the cortisone. The complement-fixing titer of the serum was positive before, during, and after administration of cortisone. The histologic structure of the precortisone test is described and contrasted with the microscopic picture of the skin at the site of the inhibited test. The discrepancy between the presence of the circulating antibodies and the inhibition of the tissue reaction is discussed.

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Clinical Notes

USE OF CORNEAL AND PHARYNGEAL REFLEX IN DERMATOLOGIC DIAGNOSIS

WILLIAM MULVEHILL, M.D.
LOS ANGELES

Consideration of the corneal and pharyngeal reflex has been a controversial issue among dermatologists for many years. In certain psychogenic diseases, such as neurotic excoriations and dermatitis factitia, many physicians believe the presence or absence of one or both of these reflexes is a valuable aid in diagnosis and differential diagnosis. Most of us have believed that the presence of a corneal and pharyngeal reflex is a normal condition in practically everyone. Generally speaking, in certain conditions neurologists also place importance upon the presence or absence of a corneal reflex. Wechsler[1] makes the statement that the absence of a corneal reflex is part of the picture of hysteria. Walker[2] refers to the value of a unilateral absence of the corneal reflex in differential diagnosis of certain cerebral conditions. As far back as 1920, Dr. Howard Fox[3] called attention in various discussions to the presence or absence of a corneal and pharyngeal reflex in dermatologic diagnosis. Conclusions were based upon the assumption that a corneal and pharyngeal reflex occurs normally in practically all persons. In 1944 Graham and Lewis[4] published a paper in which they asserted that in a large percentage of persons there is normally an absence of corneal or pharyngeal reflex. In order to help clarify the situation I have studied 479 cases, placing the patients in the following eight groups:

1.—150 normal persons who included grammar grade, high school, and university students
2.—50 psychotic patients
3.—78 patients with late syphilis including central nervous system syphilis
4.—100 patients with various dermatologic conditions, except those of psychogenic origin such as neurotic excoriation, dermatitis factitia, and localized neurodermatitis
5.—75 children aged 2 to 10 years, ward hospital patients suffering from various medical and surgical diseases
6.—7 patients with neurotic excoriation
7.—7 patients with dermatitis factitia
8.—12 patients with lichen simplex chronicus

TECHNIQUE OF TESTING REFLEX

The cornea[5] is covered by pavement epithelium four to six layers in depth which is supplied very abundantly with axis-cylinder filaments, therefore conducting only pain sense, by the ophthalmic division of the fifth cranial nerve. The motor pathway is supplied by the seventh cranial nerve. There is some divergence of opinion as to what means should be used to elicit a reflex. Anderson[6] stated that the cornea should be touched lightly with a dull instrument.

1. Wechsler, I. S.: A Textbook of Clinical Neurology with an Introduction to the History of Neurology, Ed. 4, Philadelphia, W. B. Saunders Company, 1939.

2. Walker, A. E.: Cerebral Arc of Corneal Reflex, J. Nerv. & Ment. Dis. **92**:569-578 (Nov.) 1940.

3. Fox, H.: Lupus Vulgaris (Follicular Disseminated Type), Arch. Dermat. & Syph. **1**:336 (March) 1920.

4. Graham, T. N., and Lewis, G. M.: Significance of Absent Pharyngeal and Corneal Reflexes in Cutaneous Diseases, New York J. Med. **44**:621-625 (March) 1944.

5. Morris, H.: Human Anatomy: A Complete Systematic Treatise, Ed. 10, edited by Shaeffer, J. P., Philadelphia, The Blakiston Company, 1942.

6. Anderson, W. N.: Physical Diagnosis, Philadelphia, Lea & Febiger, 1940.

Most authorities, however, including Cabot and Adams,[7] direct the use of a wisp of cotton touched lightly to the edge of the cornea. This technique I followed, with the direction that the eyes be turned away from the operator so that no possibility of a light reflex would occur. Both eyes were tested in all cases. Closure of the eye lids upon touching the cornea was considered evidence of a reflex.

There is little to be found in the literature in reference to the presence or manner of eliciting the pharyngeal reflex. The glossopharyngeal nerve supplies both the sensory and the motor pathway of the reflex. We considered the reflex absent when no discomfort was evidenced upon pressure over the posterior pharynx.

RESULTS

In the first group, 150 normal persons, 35 (23.3%) showed absence of corneal and pharyngeal reflexes, in 23 (15.3%) the pharyngeal reflex was absent, and in 47 (31.3%) the corneal reflex was absent. In 5 (3.3%) the reflex was absent in one eye and present in the other. Forty (26.6%) were normal.

In Group 2 all types of psychotic patients were included except those with major hysteria. Here there were 25 (50%) with absence of corneal reflex, 12 (24%) with absence of pharyngeal reflex, and 7 (14%) with both reflexes absent. There were no patients who showed any difference between eyes. In 13 (26%) both corneal and pharyngeal reflexes were present.

In Group 3 there were 78 patients with late syphilis. This included late latent conditions together with active central nervous system syphilis. Forty-eight patients (61.54%) had no corneal reflex, and 30 (38.46%) had no pharyngeal reflex. In 9 (11.5%) both corneal and pharyngeal reflexes were absent, and 2 patients had a reflex present on one side and absent on the other. There were no patients showing both reflexes present.

In Group 4, the results on 100 patients with various dermatologic conditions, excepting neurotic excoriation, dermatitis factitia, and lichen simplex chronicus, were as follows: 37 (37%), corneal reflex absent; 29 (29%), pharyngeal reflex absent; 14 (14%), both reflexes absent, and 34 (34%), normal. There were no patients showing any difference in the two eyes.

In Group 5 conclusions were very unsatisfactory because of our inability to get sufficient cooperation to make our tests accurate so far as the corneal reflex was concerned. There were 14 (18.6%) children who had unmistakable evidence of absence of the pharyngeal reflex.

In the group of patients with neurogenic excoriation every one had neither a corneal nor a pharyngeal reflex.

In Group 7, dermatitis factitia, four patients (57.1%) showed absence of a corneal reflex, and two (28.5%) showed absence of a pharyngeal reflex. In two (28.5%) both reflexes were absent, and one was normal (14.2%).

In Group 8, lichen simplex chronicus, there were 12 patients. Five (62.5%) had no corneal reflex, two (25%) had no pharyngeal reflex, one (12.5%) had both reflexes absent, and one, (12.5%) was normal.

COMMENT

From analyzing these figures it appears that approximately 25 to 35% of persons, both normal persons and those with diseases which are considered by dermatologists to be not of psychogenic origin, have normally a corneal and a pharyngeal reflex. The psychotic patients showed presence of reflexes in as high a percentage as did the normal group. In the group of syphilitic patients there were none presenting both a corneal and a pharyngeal reflex. Whether this is a coincidence or a result of the syphilitic injection I am not prepared to say.

In the group of children, the pharyngeal reflex was absent in approximately the same percentage as in the normal adult group. All the other groups were considerably higher, showing, possibly, that age and prolonged repeated presence of disease has some influence in obtunding sensory nerve endings. In patients with psychogenic background, it appears certain that there is a higher percentage of absence of reflexes than in all other groups; this certainly applies to neurotic excoriation, for not a single patient with this condition had either a corneal or a pharyngeal reflex. The number of patients examined in this group was, of course, small, but I believe the complete absence of any reflexes, even in this small number is significant.

7. Cabot, R. C., and Adams, F. D.: Physical Diagnosis, Ed. 12, Baltimore, William Wood & Company, 1938.

In the groups with dermatitis factitia and lichen simplex chronicus, the corneal reflex was absent in 57.1% and 62.5% respectively, and the pharyngeal was absent in somewhat higher percentage than in any other group. This fact presents evidence that could be of value in a diagnostic way, possibly in group consideration but not when patients are considered individually.

SUMMARY AND CONCLUSIONS

Four hundred and seventy-nine persons, classified in normal and disease groups, were examined for corneal and pharyngeal reflex. It was found that both a corneal and a pharyngeal reflex occur normally in health or disease in approximately 25 to 35%. In patients with skin diseases of psychogenic origin, particularly those with neurotic excoriations, the absence of a corneal and a pharyngeal reflex is of some diagnostic value, but routine dependence on the sign in any condition cannot be recommended.

10525 Santa Monica Blvd. (25).

SOLITARY SPOROTRICHOTIC GRANULOMA

BENCEL L. SCHIFF, M.D.
PAWTUCKET, R. I.

Lewis[1] states that sporotrichosis seldom remains localized to a single lesion. A perusal of the literature discloses that only two cases of solitary sporotrichotic lesions have been reported to date. Campbell,[2] in 1933, described a sporotrichotic "chancre" of five months' duration, with no satellite lesions. Graham [3] reported a second case of this type in 1941.

Recently, I have observed a similar case, which I believe may be of interest for review.

REPORT OF A CASE

L. M., a 31-year-old white farmer, born in Rhode Island, had always been in good health and gave no history of previous skin disease. Two months prior to his visit to my office, while feeding hay to his cattle, he scratched his left forearm. A week later he noticed a "pimple" on that site. Since the cutaneous manifestations continued to increase in size, the patient decided to seek medical care. Upon examination on June 8, 1950, the posterior surface of the left forearm showed a circular area, 6 cm. in diameter, studded with nodular lesions. The surface of each lesion showed pinpoint pustulation, and purulent material was readily expressed from the openings. This mass was moderately indurated but was not attached to the underlaying tissue. It was painless to touch. The rest of the forearm showed no skin abnormality, and the axillary nodes were not palpable.

Clinically, a deep fungous infection resembling a Majocchi granuloma was suspected, and material from the lesion was collected for mycologic studies. While we awaited the results of the laboratory examinations, topical application of Alibour solution (copper sulfate 2 gm., zinc sulfate 7 gm., camphor water 300 cc.) and merbromin (mercurochrome®) solution was prescribed.

MYCOLOGICAL STUDIES

Direct smear made from the pus, and stained by Gram's method, revealed no organisms. Two culture tubes containing glucose agar (Sabouraud's) were planted with specimens from direct smear and from expressed pus. On the 11th day numerous colonies were noted. The central

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1. Lewis, G. M., and Hopper, M. E.: An Introduction to Medical Mycology, Ed. 3, Chicago, The Year Book Publishers, Inc., 1948.

2. Campbell, F. K., and Plunkett, O. A.: Sporotrichotic Chancre, Arch. Dermat. & Syph. **28**:61-65 (July) 1933.

3. Graham, Paul V.: Solitary Gummatous Sporotrichosis of 2 Years' Duration, Arch. Dermat. & Syph. **43**:805-808 (May) 1941.

portion of the colonies was brown, and wrinkled, and the periphery was cream-colored and filamentous. Culture mounts revealed fine mycelia with round conidia borne on lateral branches, characteristic of Sporotrichum schenckii.

Results of an examination of the peripheral blood and routine urinalysis were within normal limits. The reaction to Wassermann and Hinton tests for syphilis were negative. When the

Fig. 1.—Solitary sporotrichotic granuloma on the forearm.

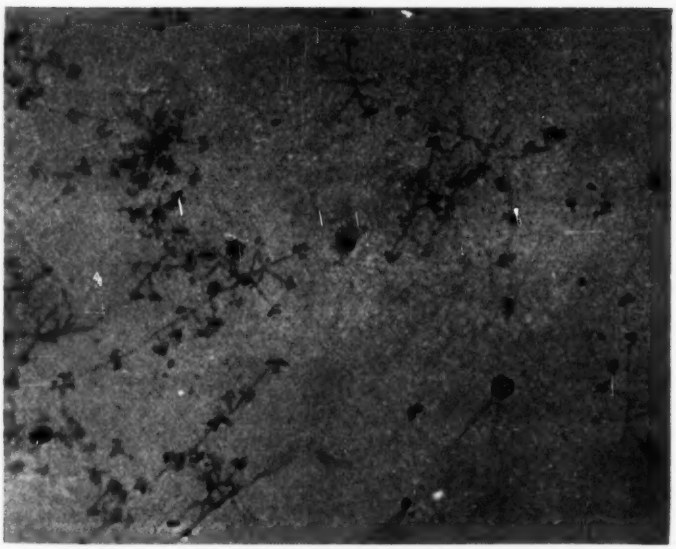

Fig. 2.—Photomicrograph of Sporotrichum schenckii showing characteristic conidia in groups from ends of the conidiophores.

diagnosis of sporotrichosis was established, use of saturated solution of potassium iodide was instituted, beginning with 30 drops orally three times daily. The patient was seen two weeks later, and the lesion on the forearm showed great improvement, with a decrease in both the purulent discharge and the size. Since the patient showed no intolerance to this treatment, the same therapy was continued for another two weeks. When seen again after this period of time,

the lesion had almost involuted. Treatment was continued, with the amount of potassium iodide decreased to 10 drops three times daily. At the end of seven weeks, the condition was apparently cured.

CONCLUSIONS

Solitary sporotrichotic lesions are a clinical rarity and cannot be diagnosed without mycologic examination. Potassium iodide is still the drug of choice in treatment of sporotrichosis.

251 Broadway.

SPOROTRICHOSIS IN COLOMBIA

MANUEL SILVA, M.D.
BOGOTA, COLOMBIA

Sporotrichosis is very common in Colombia. There are probably several thousand victims throughout the country. At the dermatologic clinic of the University of Colombia and in

Acneform lesions, a type often seen in Colombia.

private practice a patient is seen almost every week. The lesions are always on the skin and subcutaneous tissue. The diagnosis is easily made by culturing Sporotrichum schenckii in Sabouraud's medium.

The causative organism of sporotrichosis lives in a saprophytic stage on vegetables and animals. It is found in vegetables used as food and many other plants in the woods, gardens, prairies, etc. One common method of contagion is through handling the straw used in packing fragile objects. In this instance the condition is an occupational disease. It is not unusual to see a series of patients who contracted the disease by handling contaminated straw from the same packing company. This method of transmission has undoubtedly helped to spread the disease through the country. In animals the condition is seen in cats, dogs, rats, and possibly in wild animals. Dr. Albornoz has seen it on a donkey. I saw a patient in whom the disease began after a scratch from a cat.

Clinically the gummatous type, manifested by reddish or violaceous nodules along the course of the lymphatics, is the commonest form of the disease. At the onset these nodules are hard and painful; later they soften and break down discharging a gray-yellowish pus. There is no

Professor of Dermatology, University of Colombia.

lymphadenopathy. The lesions may become secondarily infected, a complication which darkens the prognosis of the disease.

There is a clinical type which seems characteristic and typical of sporotrichosis in Bogotá as I have never seen it reported elsewhere. This is the acneform type. It affects usually the face, involving the forehead, eyelids, cheeks, nose, and chin. The lesions are papules of varying sizes. Some are solid and some show a softening in the center which eventually breaks down, discharging a seropurulent material which dries into a yellowish bloody crust. In some instances the lesions are grouped and localized on the nose, chin, upper lip, etc.; in others the lesions cover most of the face, making a honeycomb appearance. The lesions resemble a clinical picture of a pyoderma. Because of their location they may in some instances be confused with acne vulgaris.

In treatment I have had excellent results with intravenous injections of strong iodine solutions, and I have found that it is well tolerated and gives better results than iodides given orally. The intravenous route has been used successfully for children, aged patients, and even pregnant women. Long-standing lesions, vegetating and verrucous, clinically resembling tuberculosis, do not respond to iodides or strong iodine solution. These conditions have been successfully treated with electrocoagulation. I have found this method extremely effective, and it constitutes a rapid and radical therapeutic procedure. The lesions are thoroughly destroyed and curetted off. After the treatment I cover the area with cotton soaked in iodine solution and apply a dressing. I have not seen relapses with this treatment. The lesions heal rapidly, with excellent cosmetic results.

CHONDRODERMATITIS NODULARIS CHRONICA HELICIS

Treatment with Bacitracin Ointment

LAWRENCE M. NELSON, M.D.
SANTA BARBARA, CALIF.

Accepted treatment for chondrodermatitis nodularis chronica helicis is either destruction or excision.[1] Recurrences are common after such treatment, and the cosmetic results are not always satisfactory. The following report is submitted because the results of the treatment used have been superior to those of any other method of treatment I have tried.

In October, 1950, a 65-year-old white woman with a painful nodule of the right ear was seen. The nodule had been cauterized and desiccated elsewhere on numerous occasions. Since the patient stated that she was sensitive to local anesthetics and since the lesion was inflamed, I prescribed bacitracin ointment for local application rather than attempting to destroy or excise the lesion at that time. One week later the pain had largely disappeared. Subsequently, all pain subsided, and the lesion decreased in size. Since then, eight additional patients have been treated with bacitracin ointment. Of these, seven have had complete or almost complete relief of tenderness, usually within a week or two. In one patient, three months elapsed before comfort was obtained. The lesions decreased in size in all patients who were followed for over two months. One patient had no relief of pain after applying the ointment for three weeks.

Six of the nine patients treated had had previous destruction or excision of the lesions followed by recurrence. Five of the patients had the treatment elsewhere; the sixth was treated by me with excision twice and cauterization on a third occasion.

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1. (*a*) Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Ed. 7, Philadelphia, Lea & Febiger, 1948, p. 584. (*b*) Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939, p. 649. (*c*) Andrews, G. C.: Diseases of the Skin for Practitioners and Students, Ed. 3, Philadelphia and London, W. B. Saunders Company, 1946, p. 712. (*d*) Woringer, F., and Zoon, J. J.: Note préliminaire sur l'abondance anormale de filets nerveux dans le nodule douloureux de l'oreille, Bull. Soc. franç. dermat. et syph. **45**:668-671 (May) 1938.

COMMENT

There is no obvious explanation for the apparent success of this type of therapy. One patient had previously treated himself with plain petrolatum and had some relief of discomfort, but the relief was not nearly as rapid nor as dramatic as occurred with the use of the bacitracin ointment. No doubt, removal of the crust and softening of the nodule by the ointment base contributed to the disappearance of discomfort, but it hardly seems that the entire picture can be explained on this basis. Inflammation does occur in chondrodermatitis; secondary infection also occurs at times,[2] but only one of the nodules appeared to be inflamed. Control of the infection, therefore, probably could not account for the result. Woringer and Zoon [1d] stated that the lesions go through cycles of inflammation and cicatrization; however, one of the lesions had been present practically unchanged for 20 years, and most of them (aside from the time during which they subsided after destruction or excision) were of several months' or years' duration. It is unlikely that the eight lesions underwent spontaneous cicatrization at just the time that the bacitracin ointment was prescribed.

SUMMARY

Eight of nine patients with chondrodermatitis nodularis chronica helicis treated by topical application of bacitracin ointment had relief of the tenderness characteristic of the condition. The treatment was unsuccessful in one patient.

30 W. Arrelaga St.

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2. Ormsby and Montgomery.[1a] Woringer and Zoon.[1d]

Correspondence

TREATMENT OF VITILIGO

To the Editor:—I have received numerous inquiries about my discussion in the ARCHIVES (**63**:786 [June] 1951) of the treatment of vitiligo.

In 1947, I. R. Fahmy and Hamed Abu Shady isolated from the fruits of Amni majus two crystalline compounds, to which the names amoidin ($C_{12}H_8O_4$) and ammidin ($C_{16}H_{12}O_4$) were given. These are really bitter substances and not alkaloids, as they do not contain a nitrogen group.

The available literature to date is as follows:

1. Fahmy, I. R., and Abu Shady, H.: The Isolation and Properties of Ammoidin, Ammidin, and Majudin and Their Effect in the Treatment of Leucoderma, *J. Pharm. & Pharmacol.* **21**:449-503, 1948.

2. El Mofti, A. M.: A Preliminary Clinical Report on the Treatment of Leucoderma with Amni Majus Linn, *J. Roy. Egyptian M. A.* **31**:651-665 (Aug.) 1948.

3. El Mofti, A. M.: Further Clinical Observation, personal communication to the author, to be published.

4. El Hefnaoui, H.: A Preliminary Clinical Report on the Treatment of Leucoderma with Meladinin Tablets and Meladinin Paints, *Trudeau Rev.*, June, 1950.

5. Abd-El-Malek, A. I.: A Preliminary Clinical Report on the Treatment of Leucoderma with Meladinin Tablets and Meladinin Paints, *Gaz. Faculty Med.* **16**:57-64 (May-Aug.) 1950.

6. Elwi, A. M.: Report on Pathological Lesions Resulting from the Administration of Xanthotoxine and Imperatorine to Guinea Pigs, *J. Roy. Egyptian M. A.* **33**:773-781, 1950.

As for my own experience with this method of treating vitiligo, I should like to point out two things:

(*a*) Good results are obtained with the medication when the leucoderma is located on the trunk. The extremities, hands and feet especially, need more than four months to produce pigmentation.

(*b*) The crude plant preparations are certainly more powerful, owing to the presence of majudin, which seems to enhance the effect of the other two bitter substances (ammoidin and ammidin), and I hope that the firm producing the medication will soon be able to incorporate majudin in its product.

The actual tablet has the following content:

	Gm.
Ammoidin *	0.010
Ammidin †	0.005
Starch	0.100
Lactose	0.075
Talcum	0.020
Total	0.210

* Active principle extracted from Amni majus, melting point 145 C.
† Active principle extracted from Amni majus, melting point 102 C.

Contents of the alcoholic paint are as follows:

	Cc.
Ammoidin	0.75
Ammidin	0.25
Acetone	10.00
Propylene glycol	10.00
90% alcohol v/v, enough to make	100.00

In treatment, one tablet (0.21 gm. by weight) is administered three times a day, after meals, for a period of two to three months, on the average. During this period one-week rests, at intervals of three weeks, are allowed. At the same time, the alcoholic paint is applied two or three times a week, followed each time by ultraviolet irradiation for 5 to 10 minutes. The application is done with a painting brush or with a piece of cotton on a glass rod. The preparations I have used are "meladinin" tablets (for oral use three times a day) and "meladinin" paint (for local application, to be followed by ultraviolet irradiation, twice weekly), both products of Memphis Chemical Laboratories, Cairo, Egypt.

A few days after the treatment is begun, the leucodermic areas become inflamed, as shown by the development of erythema and vesiculation. At this stage the dosage of tablets and irradiation must be regulated in order to avoid severe vesiculation and unnecessary blistering of the patches, which, if it occurs, will necessitate a temporary arrest of the vitiligo treatment and dealing with the patches as ordinary burns.

Pigmentation at the periphery of the patches and islands of pigment generally make their appearance 7 to 15 days after the occurrence of the local inflammatory reaction. Peripheral invasion and central coalescence of pigments are often marked features after each subsequent local inflammation.

Treatment must be continued until complete regression in the patches occurs. Patches of the vitiligo that reappear in old previous sites were always patches that did not completely regress at the first trial of the drug.

MAGDI SEKLA, Zeitoun, near Cairo, Egypt.

Society Transactions

BRONX DERMATOLOGICAL SOCIETY

Charles R. Rein, M.D., President
Henry Silver, M.D., Secretary
March 15, 1951

Hypertensive Ischemic Leg Ulcers Treated with Priscoline.® Presented by DR. NORMAN B. KANOF.

L. S., a white woman aged 59, had ulcerations on the legs, first about six years ago and again in 1949, which responded quickly to local measures. They seemed to follow accidental minor trauma. The most recent episode began in the spring of 1950, again following minor injury, but failed to respond to local measures and were painful, frequently keeping her awake at night.

Hypertension has been present for 20 years, with levels of blood pressure up to 190 mm. of mercury and occasional dizzy spells. An episode of "sudden blindness" in the right eye 10 years ago cleared gradually. A "stroke" six or seven years ago affected the right side and has since cleared. There has been occasional ankle edema in the last six or seven years, with some "sticking pain" in the calves on walking.

This patient was admitted to the University Hospital of the New York University-Bellevue Medical Center on Aug. 24, 1950, with ulcers on the anterior aspect of each lower leg. A good dorsalis pedis pulse was palpable on the right leg and none on the left. Popliteal pulses were palpable. There was no evidence of venous insufficiency. There was some proptosis of the right eye with some jerkiness of extraocular movements on the right. The fundi revealed tortuous arterioles with no hemorrhages or exudates.

The results of glucose and galactose tolerance tests were normal. The total serum protein was 7.8 gm. per 100 cc. (normal, 6 to 8 gm.), with 4.66 gm. of albumin (normal, 4 to 5 gm.) and 3.2 gm. of globulin (normal, 2 to 3 gm.). The basal metabolic rate was + 21%. Repeated examinations of the urine showed an inability to concentrate above 1.012. Chemical examination of the blood showed 41 mg. of nonprotein nitrogen, 26 mg. of urea nitrogen (normal 10 to 15 mg.), 2 mg. of creatinine (normal 1 to 2 mg.), 290 mg. of serum cholesterol (normal 160 to 230 mg.), and 175 mg. of cholesterol esters per 100 cc. of blood (normal 100 to 150 mg.). In the phenolsulfonphthalein test only 21% of the dye was excreted in two hours (normal over 50%). The erythrocyte sedimentation rate was 77 mm. per hour (normal 15 mm.).

In the diagnosis of hypertensive ischemic ulcers, the medical service and the consultant for peripheral vascular diseases concurred.

Local treatment to the ulcers during hospitalization included potassium permanganate soaks and silver nitrate soaks; ointments containing water-soluble chlorophyll derivatives (chloresium®) and scarlet red; compresses with 4% urea, 4% urea in aquaphor® (an oxycholesterol-petrolatum ointment base), and aluminum acetate-zinc oxide, and adhesive taping of the ulcer edges.

Treatment with priscoline,® 25 mg. three times a day by mouth was begun on Sept. 6, 1950. There was dramatic relief of pain in a few days, and healing of the ulcers progressed slowly with the various local remedies mentioned.

The patient was discharged with the ulcers completely closed on Nov. 9, 1950, after being hospitalized for 10 weeks, and has been followed in the outpatient department at the Skin and Cancer Clinic since then.

DISCUSSION

DR. FRANZ J. HERRMANN: In a patient with Raynaud's disease of the right index finger, associated with ulceration of the tip and recalcitrant to other forms of therapy, miraculous subsidence of all changes was attained within a few weeks with priscoline.®

DR. FRANK E. CROSS: It is not common to see this bilateral almost symmetrical type of ulcer. The fact that the patient responded to priscoline® is a therapeutic test in favor of the diagnosis. Prior to treatment he suffered exquisite pain, which disappeared under treatment. The ulcers in the case presented did not heal promptly, which is also my experience.

DR. CHARLES WOLF: The therapeutic result is excellent. It would have been instructive had photographs of the condition been shown before treatment was instituted. How does priscoline® act?

DR. NORMAN B. KANOF: I am sorry that photographs were not taken before treatment was begun. Priscoline® is thought to produce vasodilatation by its adrenergic and sympathetic blocking action upon the vascular receptors, as well as by a direct vasodilating effect on the small blood vessels. The drug produced dramatic relief of pain in this case, but healing was prolonged, nevertheless, requiring 10 weeks of hospitalization.

Incontinentia Pigmenti (Bloch-Sulzberger). Presented by DR. CHARLES R. REIN and (by invitation) DR. A. I. WEIDMAN.

J. S. is an infant girl aged 2½ years. Her father suffers from hay fever. There is no history of pigmentary anomalies or mental disturbance in the family. The mother states that about two days after birth there appeared on the baby's skin a "pink blistery rash" which remained for six weeks and left a residual pigmentation and "lines."

The child is well developed and fairly well nourished. Examination of the skin reveals pigmented areas distributed mostly over the trunk and extremities but sparing the face. The pigmentary disturbance is bizarre; in some areas it forms a network, in others it assumes an irregular pattern comparable to branches of trees, spiders, or feathers.

Ophthalmologic examination was made by Dr. L. R. Lang. The visual acuity could not be determined because of the patient's age. Retinoscopic examination, however, revealed a high degree of myopia. Examination of the fundus was extremely difficult. Dr. Lang was able to see the optic disc, which was pale and showed a marked degree of stretching, characteristic of myopia. Throughout the fundus were numerous patches of pigment, varying in size, situated in either the retina or the choroid.

A biopsy specimen was taken from a pigmented lesion on the patient's thigh and examined by Dr. Max Jessner. The horny layer was lamellous and somewhat enlarged. The epidermis was normal except that no pigment could be found in the basal-cell layer and higher up. There was some inflammatory infiltration around the vessels and in the uppermost part of the cutis, and one could see in places massed pigment which was partly contained in the chromatophores. Where it was more clumpy, it was impossible to make out whether it was intracellular or extracellular. The histologic diagnosis was compatible with incontinentia pigmenti.

Serologic reactions for syphilis were negative in the father, mother, and patient. Psychologic examination was made by Miss Stephanie Dudek. The Stanford-Binet test of intelligence (Form L) and the Rorschach test of personality were employed. The general impression was of a normal, relatively spontaneous child of average intellectual development.

Dental examination was made by Dr. A. G. Beck, who reported that the child represented a retarded development of at least six months. The teeth were crowded, showed malocclusion, were underdeveloped in size, and had a white chalk-like appearance. The upper and lower arches were small and narrow and seemed to correspond to the narrow structure of the face. The palate showed a high narrow vault, suggestive of a tendency to arrested cleft palate, with lateral walls deeply convex towards the medial line. There was no evidence of pathologic changes of the soft tissues. The child gave the impression of a mouth breather, which may be due to the narrow nasal passages caused by the crowded arch.

DISCUSSION

DR. MAX JESSNER: This is one of the rare cases of incontinentia pigmenti.

DR. PAUL GROSS: This is an uncomplicated case of incontinentia pigmenti. Are the hair changes of the scalp part of the picture?

DR. A. I. WEIDMAN (by invitation): This rare pigmentary affection has a familial and, perhaps, also hereditary tendency manifesting itself, either directly, as in Naegeli's cases, or in a tendency toward development of ectodermal defects, as in Sulzberger's cases. This answers the question of Dr. Gross concerning the ectodermal defects in our patient who presents malformation of hair and teeth.

As far as the pathogenesis is concerned, inflammation, trauma, or other intrauterine or extrauterine factors cause damage to the basal cells, which leads to "incontinence" or dropping

of the pigment into the corium where it forms deposits of melanin in the chromatophores. Sulzberger assumed a permeability of the cell membrane to melanin. As to the course, in some patients there was a spontaneous remission, while in others the condition had a tendency to clear after a variable period of time, as reported by Siemens, Bloch, Sulzberger, and many others. The melanin which drops from the incontinent epidermis can remain unaltered for many years in the corium, as demonstrated by Miescher, who injected melanin into the corium and was able to detect the pigment in the chromatophores after many years.

There are many synonyms which lead to confusion. Siemens called it "melanosis corii degenerativa," which is a pathogenetic name. Levin called it "nevus reticularis et pigmentosus," and Naegeli proposed the name "familial chromatophore nevus."

Finally an interesting observation is worth mentioning: After an upper respiratory infection for which penicillin, streptomycin, and aureomycin had been administered, there developed an inflammatory reaction, limited to the areas affected by the pigmentary process. This was manifested by elevation of the pigmented spots which was more accentuated on the lower extremities.

Juxta-Articular Nodes; Etiology(?). Presented by Dr. Arthur B. Hyman.

J. M., a white handyman aged 40, is engaged in vigorous manual labor, i. e., laying bricks, handling asbestos, etc. There is no history of rheumatism and no evidence of syphilis.

On the lateral surface of the right index finger at the interphalangeal joints there are two firm, nontender, movable nodules the size of a pea. There are similar nodules on the lateral aspects of the left middle finger. On the right middle finger, over the middle joint, is a similar lesion the size of an almond, and there is a lesion on the anterior surface of the finger, in the same location, the size of a cherry, as well as a soft almost fluctulant nodular lesion on the extensor aspects of the forearm, just distal to the elbow.

The histologic examination of a section showed numerous areas of homogenization of the cutis masses, part of which were basophilic and probably contained calcium. Surrounding each of these oval and irregularly shaped homogenized areas there were radiating, coarsely vacuolated, encapsulated cells which merged into the surrounding or normal connective-tissue bundles. Within more normal connective-tissue bundles, the capillaries showed thick walls, and in many of them the lumens were almost obliterated. Examination of another section showed the same picture but considerably more advanced, and there was breakdown in the center of one of the homogenized areas. Around the connective tissue, in some places, was an outstanding fibroblastic reaction.

DISCUSSION

Dr. Frederick Reiss: Teller and Jessner have both been prominently associated with the investigation of this condition. Teller stressed its relationship to syphilis; Jessner inoculated rabbits with material from nodes and produced syphilis. All cases that I have seen were associated either with syphilis or yaws. Serologic reactions for syphilis in Dr. Hyman's patient were negative. Further investigation is indicated along the lines of Dr. Nelson's newer work.

Dr. Robert A. Nelson Jr. (by invitation): I should like to get a section of the tissue. In spite of the fact that significant results in biopsies were obtained in only a few cases, we have had pretty good success in demonstrating spirochetes in gummas from the liver, stomach, etc. It is important to do biopsies, but, personally, I believe that the treponemal immobilization test should serve us best.

Dr. Irwin I. Lubowe: A patient previously presented before this society, with this condition of 10 years' duration, was successfully treated, with complete disappearance of the lesions.

Dr. Mabel G. Silverberg: It should be noted that the patient presented has rheumatic fever.

Dr. Max Jessner: The only positive inoculations until now were obtained from two patients in whom the condition was of about one year's duration. Interesting is the fact that antisyphilitic treatment causes the disappearance of nodes which, histologically, consist of dense fibrotic masses.

Dr. Arthur B. Hyman: Some syphilitic nodosities have been reported in which serologic reactions were negative. Yet, such cases have responded to antisyphilitic therapy. We have no reason to assume that the patient has syphilis; but I shall accept Dr. Nelson's suggestion and submit a specimen for the treponemal immobilization test. Nodosities have been described in

connection with other diseases, such as yaws, and leprosy, in which they show lepromatous tissue histologically, xanthomatosis, and rheumatism, as well as in scleroderma, acrodermatitis chronica atrophicans, gout, etc. In all these diseases repeated trauma would appear to be a precipitating factor. In this patient also there was trauma, but I can find no background of any of the latter diseases mentioned. Attempts at causal differentiation on the basis of the nodules being in or under the skin are unsuccessful. This patient has both types and also some on the palms which is a rare site, though Dr. Jessner has seen such cases. On histologic grounds the syphilitic type may show gumma formation to differentiate it from the rheumatic type. The former rarely soften and break down; the latter not uncommonly liquefy in the center. In this case there were lesions which were soft and lobulated, simulating a lipoma or cyst. To reiterate, we have here the element of trauma but are unable to trace the disease background for the nodosities.

Xanthoma Disseminatum (Juvenile). Presented by DR. JOHN GARB.

P. M., a boy aged 6½ years, registered at the New York Skin and Cancer Hospital on Feb. 20, 1951, presenting an eruption of about six years' duration. His paternal grandmother had pigmentation on her arms. His half-brother, aged 3 years, has no similar disorder. The patient has had only measles, tonsillitis, and common colds. The boy is intelligent and appears healthy. He has a poor appetite, although he weighs 50 kg. and measures 125 cm. in height. There are no subjective symptoms and no history of polyuria.

At the age of 8 months a few light-brown soft spots were noticed on the face. A few months later more lesions appeared on the malar regions, under the chin, on the forehead, and later on the back. They became darker and raised but not larger. At that time a lesion on the back was removed for histologic examination and diagnosed as molluscum contagiosum. Most of the growths were destroyed by electrodesiccation; others "could not be touched." At 3½ years of age, two months after he had measles, some of the lesions that had been removed reappeared. More lesions appeared gradually in groups on the arms and, within six months, over the trunk. No new lesions seemed to develop since last year, and none seemed to disappear.

The patient presents generalized brownish spots varying in size from a pinhead or a match head to a bean. One lesion on the flexor surface of the right thigh measures 4 by 1 cm. The scalp, oral mucosa, hands, and legs are not involved. The lesions are discrete, many of them closely grouped. On the shoulders and sides of the neck they are raised and yellowish, and some are herniated, with atrophic fine wrinkling surfaces. They are painless, nontender, and do not fade on diascopic pressure. The liver and spleen are not palpably enlarged.

The urine and lipid partition showed no abnormalities. The hemogram showed 3,500,000 erythrocytes, with 70% hemoglobin, and otherwise normal findings except for 4% eosinophiles.

From a histologic section, taken on March 1, 1951, from a lesion on the right arm Dr. C. F. Sims diagnosed a xanthoma. The epidermis was thin, and the rete pegs were rudimentary. There was pronounced pigment in the basal-cell layer. The upper cutis presented foam and Touton giant cells. There was a reaction about the vessels of the upper cutis. The fat stain showed deposits throughout the cutis.

DISCUSSION

DR. FRANCES PASCHER: This is a striking case that brings up a number of controversial points. The lesions first appeared when the child was 6 months old, increased in number, but are now receding. The course suggests nevoxanthoendothelioma as a possible diagnosis. There is some question, however, as to whether or not the latter is a clinical entity, since some conditions so diagnosed were later shown to be examples of juvenile xanthoma, or should it be regarded, as Thannhauser suggested (Thannhauser, S. J.: Lipidoses: Diseases of the Cellular Lipid Metabolism, Ed. 2, N. Y., Oxford University Press, 1950) as the monosymptomatic form of Schüller-Christian disease?

DR. FRANZ J. HERRMANN: This type of juvenile xanthoma disseminatum is characterized by its definite histiogenic pathogenesis in situ. Contrary to other forms of juvenile xanthoma, there is no lipid dyscrasia in the blood. The condition has been described by various investigators, e. g., M. Jessner, W. Siemens, and also E. Nathan and I. Spontaneous healing may occur. According to the classification of S. Thannhauser and his group, the condition is related to Schüller-Christian disease because of the histiocytic origin of both processes.

DR. JOHN GARB: Xanthoma disseminatum (juvenile) seems to be the monosymptomatic variety of Schüller-Christian's syndrome (eosinophilic granuloma, lipid granuloma). Thannhauser is of the opinion that these cases run a benign course and may disappear completely in later life, although there are no complete follow-up reports in the literature to confirm his opinion. These children should, therefore, have a yearly follow-up examination with roentgenograms of bones and lungs. Cutaneous lesions are rarely encountered in patients with typical triad of Schüller-Christian syndrome, with diabetes insipidus, exophthalmos, and multiple defects of the bones, especially of the cranium (Hand, A.: *Am. J. M. Sc.* **162**:509, 1921). Only in atypical cases are cutaneous lesions called xanthoma disseminatum occasionally found (Lever, W. F.: Histopathology of the Skin, Philadelphia, J. B. Lippincott Company, 1949, p. 222). Roentgenologic examination of the lungs was ordered and later reported upon as normal. However, there may be small foci in bones or organs which could not be detected by roentgenologic examination.

A Case for Diagnosis: Nevus? Folliculitis Ulerythematosa Reticulata? Presented by DR. VICTOR H. WITTEN

Lymphocytoma. Presented by DR. DAVID B. BALLIN.

Dermatomyositis with Subcutaneous Calcification. Presented by DR. ABRAHAM J. ORFUSS and (by invitation) DR. M. A. BELSON.

Pityriasis Rubra Pilaris. Presented by DR. ALEXANDER A. FISHER.

Lymphangioma of the Upper Lip. Presented by DR. ALEXANDER A. FISHER.

A Case for Diagnosis: Lichen Planus? Black Hairy Tongue? Presented by DR. ALEXANDER A. FISHER.

Syringoma. Presented by DR. HARRY B. FEILER.

Erythema Induratum and Papulonecrotic Tuberculid. Presented by DR. ABRAHAM J. ORFUSS.

Extensive Keloid with Partial Spontaneous Involution. Presented by DR. ELLEN REINER.

Disseminated Granuloma Annulare. Presented by DR. JOHN GARB.

Sarcoid Occurring in the Previous Site of Injury. Presented by DR. IRWIN I. LUBOWE and (by invitation) DR. SIDNEY ROBBINS.

Bilateral Nevus Flammeus. Presented by DR. FRANK E. CROSS.

CENTRAL STATES DERMATOLOGICAL SOCIETY

A. E. Schiller, M.D., *Presiding Officer*

R. H. Holmes, M.D., *Recorder*

April 28, 1951

Generalized Amyloidosis. Presented by the Department of Dermatology, University of Michigan.

Localized Cutaneous Amyloidosis. Presented by DR. A. E. SCHILLER, Detroit, and DR. H. H. HOLMAN, Detroit.

L. B., a white man aged 56, had various medical and surgical treatment for duodenal and gastric ulcers since 1915. In none of the resected material was amyloid tissue ever found.

Physical examination shows excoriated reddish-brown papules, with underlying lichenification and brawny pigmentation.

There were no abnormalities revealed by general laboratory examination. A sulfobromophthalein sodium test revealed 35% of the dye retained at a 5-minute interval and less than 5% retained after 30 minutes. Reaction to Congo red injection was positive. The diagnosis from the biopsy was reported as amyloidosis cutis, lichenoid.

DISCUSSION OF TWO PRECEDING CASES

DR. HERMAN PINKUS, Detroit: I wish to suggest a technical feature in amyloidosis. Leave the paraffin sections, just as they are, in the methylrosaniline chloride solution for a few hours. Let them dry, dissolve out the paraffin, and embed them in Canada balsam. Even without doing this specific stain, I find that with Giemsa stain alone the amyloid tissue usually is identified, as it will stain light blue while ordinary hyalin material will stain pink.

Reticuloendotheliosis; Schüller-Christian Syndrome. Presented by the Department of Dermatology, University of Michigan.

M. B., a white girl aged 46 months, was seen first at the age of 27 months for a chronic dermatitis of the scalp, ears, vulva, and perianal region. It was noted that she had an excessive

thirst. A routine chest roentgenogram incidentally revealed a cystic tumor in the right humerus. On admission to the hospital a few months later, a soft nontender fluctuating tumor mass, about 1 cm. in diameter, was palpable in the frontal region of the skull. The liver was palpated 1 cm. below the right costal margin. A crusted scaly patchy dermatitis was scattered on the scalp, and there were eroded papules about the anus and vulva, with erythema, fissuring, and thickening of the skin. The laboratory reported these findings: hemoglobin, 12 gm.; red blood cell count, 5,900,000; white cell count, 11,200, with 50% polymorphonuclear leucocytes, 42% lymphocytes, 8% eosinophils, and fasting blood sugar 86 mg. per 100 cc. The Kahn reaction for syphilis was negative. Roentgenograms showed advancement of lytic lesions in the skull and humerus. The report on a biopsy of a vulvar lesion was "large reticuloendothelial cells and eosinophils in the papillary and subpapillary layers of the dermis."

DISCUSSION

DR. F. W. LYNCH, St. Paul: This child had many of the classic findings. There were seborrheic-dermatitis-like lesions, presumably diabetes insipidus, bony tumors, and granulomas. I noted no evidence of disturbance of the lipoid metabolism, but that is not necessary for this diagnosis.

Granulosis Rubra Nasi. Presented by the Department of Dermatology, University of Michigan.

H. T., a white girl, 9 years old, has had redness and hyperidrosis of the tip of her nose for five years. This is worse when she is warm or after exposure to the sun. There is no other seasonal variation. She is said to have a 10-year-old brother with similar findings.

DISCUSSION

DR. LEON GOLDMAN, Cincinnati: The differential diagnosis is between discoid lupus erythematosis and a solar dermatitis. I favor the latter diagnosis.

A Case for Diagnosis: Leprosy? Presented by the Department of Dermatology, City of Detroit Receiving Hospital.

O. A., a Mexican woman aged 21, had her ears pierced for earrings five years ago. A year later, without her having worn earrings, both lobes became swollen and dark red. Lesions of this same type progressed on the cheeks toward the center of the face. There are no subjective symptoms. The objective lesions are granulomatous, nontender, nonulcerative, and irregularly outlined. The anterior borders are more erythematous than the remainder, which is darker and has some pigmentation. The anterior cervical nodes are palpable. Penicillin and x-ray therapy have not affected the condition. Usual laboratory findings are within normal limits.

DISCUSSION

DR. J. W. JORDON, Buffalo: The histologic picture is that of an infectious granuloma. The negative reaction to the tuberculin test does not adequately rule out tuberculosis. Leprosy must still be considered.

DR. C. MOPPER, Detroit: There was no response to x-ray treatment.

DR. A. E. CURTIS, Ann Arbor, Mich.: Our pathologist thought the sections were compatible with leprosy.

Blastomycosis. Presented by the Department of Dermatology, University of Michigan.

DISCUSSION

DR. A. C. CURTIS, Ann Arbor, Mich.: This patient was at one time treated with radioactive iodine. There was no concentration of the iodide in the lesions, and no effect on the lesions was observed.

Coccidioidomycosis, Primary Inoculation. Presented by the Department of Dermatology, University of Michigan.

W. D., a white youth, aged 18, spent the summer of 1950 on an Arizona ranch. In September he noted a small boil on the medial aspect of the left thigh. Sulfonamides, penicillin, and

chloramphenicol (chloromycetin®) failed to affect the resulting ulcer or its drainage. Two months later the left inguinal nodes enlarged to the size of an egg.

Cultures revealed typical colonies of Coccidioides immitis.

DISCUSSION

DR. A. C. CURTIS, Ann Arbor, Mich.: This is only the third case known of primary inoculation of coccidioidomycosis.

Malignant Tumor of Left Testicle with Metastasis to Aortic Lymph Nodes; Acne Vulgaris of Neck, Scalp, and Chest. Presented by the Department of Dermatology, University of Michigan.

DISCUSSION

DR. A. L. WELSH, Cincinnati: This case is interesting because it emphasizes the factor of androgen in the production of acneform eruptions.

Acquired Porphyria. Presented by the Department of Dermatology, University of Michigan.

DISCUSSION

DR. L. BRUNSTING, Rochester, Minn.: I disapprove of the term "acquired porphyria." Like epidermolysis bullosa and xanthomatosis, although the symptoms may develop in adult life, it is on a hereditary basis. A study of the family is necessary in each case to establish the genetic pattern.

Lymphoblastoma Cutis. Presented by DR. L. W. SHAFFER and staff of City of Detroit Receiving Hospital.

Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi. Presented by the Department of Dermatology, University of Michigan.

Necrobiosis Lipoidica Diabeticorum. Presented by the Department of Dermatology, University of Michigan.

Sarcoid of Boeck. Presented by the Department of Dermatology, University of Michigan.

Sarcoidosis. Presented by DR. LOREN W. SHAFFER and staff of City of Detroit Receiving Hospital.

Sarcoid of Boeck, with Eye Involvement. Presented by the Department of Dermatology, University of Michigan.

Sarcoid of Boeck; Late Latent Syphilis. Presented by the Department of Dermatology, University of Michigan.

Sarcoid(?); Foreign Body Granuloma(?). Presented by DR. E. A. HAND, Saginaw, Mich.

Eosinophilic Granuloma. Presented by DR. E. A. HAND, Saginaw, Mich.

Torulosis. Presented by the Department of Dermatology, University of Michigan.

Multiple Lentigenes; Psychoneurosis. Presented by the Department of Dermatology, University of Michigan.

Generalized Lentigenes; Psychoneurosis with Anxiety Depression. Presented by the Department of Dermatology, University of Michigan.

A Case for Diagnosis: Lichen Planus? Presented by the Department of Dermatology, University of Michigan.

Pemphigus Erythematosus (Senear-Usher Syndrome). Presented by the Department of Dermatology, University of Michigan.

Dermatitis Herpetiformis. Presented by the Department of Dermatology, University of Michigan.

Dermatomyositis with Calcinosis Universalis. Presented by the Department of Dermatology, University of Michigan.

Porphyria and Scleroderma. Presented by the Department of Dermatology, University of Michigan.

CHICAGO DERMATOLOGICAL SOCIETY

Stephen Rothman, M.D., *President*

James R. Webster, M.D., *Secretary*

March 21, 1951

Lichen Striatus. Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. E. J. VANSCOTT, Buffalo.

C. M., a 2½-year-old white girl had a "scaling" eruption on the flexor surface of the right leg one year ago. It remained restricted to the lower leg, lasted for a few weeks, and then disappeared spontaneously. The pediatrician thought it was due to a vitamin deficiency.

The present outbreak started about five weeks ago and has spread in linear fashion from the ankle region to the leg and thigh. The eruption is slightly pruritic.

Physical examination two weeks ago revealed no abnormalities except for the skin manifestations, which consisted of linearly arranged, flat-topped, nonerythematous papules on the

posterior aspect of the right leg. These papules tended to group in some areas and form plaques. During the past week the eruption has subsided somewhat, and the papules have become more confluent. The characteristics of the original eruption, however, are still recognizable.

Histologic section from a biopsy specimen taken on March 6, 1951, shows a loosely adherent moderate hyperkeratosis and minimal parakeratosis. The Malpighian layer is slightly acanthotic and in some areas is invaded by scattered round cells from below. The corium is essentially normal except for a perivascular infiltrate of round cells and a few histiocytes. This is most prominent in the subpapillary layer but is seen also in the midcorium.

DISCUSSION

DR. C. W. FINNERUD: This disorder is extremely variable in the course that it runs, with or without treatment. In some cases the condition lasts for months and in some it clears within a very few weeks. The most interesting feature of this case is that the patient had the disorder previously and it cleared entirely. Then it recurred on the same extremity.

DR. M. R. CARO: I agree with the diagnosis of lichen striatus. Like Dr. Finnerud I was struck by the deviation from the usual in that the lesions recurred after having once disappeared spontaneously. There are two other features here that are unusual for lichen striatus. One is the involvement of the lower extremity. Most of the patients reported by Dr. Senear and me had lesions on the upper extremity, while most disorders involving the lower extremity turned out to be something else. In most of our cases also the lesions were in very narrow bands. I have never before seen a patient in whom the band was wide enough to go more than halfway around the thigh. Nevertheless, I agree with the diagnosis of lichen striatus in this case.

DR. E. J. VANSCOTT, Buffalo (by invitation): In the discussion of the paper by Dr. Senear and Dr. Caro, Dr. Ebert and Dr. Fox said they had seen several cases in which there was an eruption on the lower extremity.

A Case for Diagnosis: Disseminated Neurodermatitis? Presented by DR. EDWARD A. OLIVER and staff.

F. B. W., a 56-year-old white man, was admitted to the Veterans Administration Hospital, Hines, Ill., on March 16, 1951, as a transfer from the Veterans Administration Hospital in Memphis.

The patient states that he first noticed slight, fine, chaff-like scaling from the trunk in 1939 when undressing at night. Up to 1944 there had been a gradual increase in the amount of scaling, and the trunk and upper outer thighs had become slightly reddened and itchy. By 1946 the eruption involved the entire body except for the face and scalp; the redness, scaling, and itching were all more pronounced. In October, 1947, he was seen by Dr. Paul G. Reque of Birmingham, Ala., and the clinical and microscopic diagnosis at that time was "lichen sclerosis et atrophicus." His condition gradually became progressively worse in spite of various forms of systemic and local therapy. He was hospitalized frequently and for indefinite periods at various private and Veterans Administration hospitals in Louisiana, Mississippi, and Alabama. In January, 1950, he began to have recurrent episodes of chills and fever which did not respond to the usual forms of therapy. Along with the increasing severity of the dermatitis, there was a progressive mental depression and emotional instability.

He was admitted to the Veterans' Administration hospital in Memphis, Tenn., on March 4, 1950. He continued a stormy course, with recurrent chills and fever, a severe exfoliating dermatitis with marked hyperkeratotic and verrucous involvement of the hands, wrists, ankles, and feet. At no time did he have vesicles, bullae, or any exudation. All known forms of systemic therapy, including antibiotics, and local therapy, including x-ray treatment, proved ineffective. A biopsy specimen on Aug. 15, 1950, was reported by Dr. Wilbert Sachs as showing "chronic dermatitis, possibly a disseminated neurodermatitis." Dr. Fred D. Weidman also examined the slide and reported "nonspecific dermatitis."

Since the patient had not responded to previous treatment, cortisone therapy was begun on Nov. 24, 1950, with 100 mg. every 8 hours for the first day, 100 mg. every 12 hours the second day, and then 100 mg. daily. As the patient became afebrile and the eruption began to subside, the dosage of cortisone was gradually reduced. He is now receiving 30 mg. every other day. The mental depression and emotional instability also responded remarkably to the cortisone therapy.

The results of routine laboratory studies, blood-chemistry and liver-function tests, and chest roentgenograms were within normal limits. In March, 1950, there was a reversal of the ratio of albumin to globulin, but this was soon corrected. Malarial smears, blood cultures, scrapings and cultures for fungi, examination of sternal marrow for L. E. cells, and agglutination tests all revealed no significant abnormalities.

DISCUSSION

DR. HARRY R. FOERSTER, Milwaukee: This case is reminiscent of ones we saw more frequently at our meetings years ago. The condition is a scaling erythroderma of the type that may eventuate in mycosis fungoides. There may have been some temporary involution following corticotropin (ACTH) therapy. I believe it is only temporary. Differentiation from parapsoriasis maculata en plaque must be considered but often cannot be made until after a long period of observation, though severe itching, pronounced scaling, and infiltration of long standing favor consideration of a premycotic phase of mycosis fungoides. I saw a somewhat similar case a few weeks ago in which a diagnosis of parapsoriasis maculata en plaque was tenable and had been made on clinical and histologic findings several years ago. A recent biopsy showed the features of early mycosis fungoides. I suggest a biopsy of an eczematous plaque on the buttocks in the patient under discussion, and if it fails to show features of mycosis fungoides biopsies should be repeated from time to time.

In this case poikiloderma atrophicans vasculare may also be considered because of some areas of reticulated pigmentation, vasodilation, and atrophy, suggestive of x-ray changes, though not well defined.

DR. STEPHEN ROTHMAN: I should like to suggest the diagnosis of pityriasis rubra (Hebra). Although there is some doubt whether there is such an entity, it happens time and again that an erythroderma is present for many years without a lymphoblastoma developing, as in this man's case. Telangiectases and atrophy as described by Hebra are particularly characteristic clinical features.

DR. O. H. FOERSTER, Milwaukee: I was as always much interested in Dr. Rothman's remarks. In the cases of pityriasis rubra of Hebra which I have seen the disease was attended in late stages by considerable atrophy, shrinking, and retraction of the skin, often with ectropion and fixation of the fingers, conditions which are absent in this patient. The impression I have is that this case may belong in Brocq's parapsoriasis group. The reticulation makes us think of parapsoriasis variegata, as first described by Unna, Santi, and Pollitzer. This is a disorder of great rarity, and even those most competent to recognize it have not agreed on the diagnosis in the same case. It is identical with lichen variegatus of Crocker and parapsoriasis lichenoide papulata of Brocq. The probable existence of transitional forms increases the difficulty in diagnosis. Incidentally, if I remember rightly, at least one of the cases originally published by Unna was presented 10 or 12 years later at a dermatologic congress in Dublin and was then diagnosed as mycosis fungoides. It is now well known that parapsoriasis of the disseminate type, of which we see many more cases than of the rare lichenoid variety, may last for years and then terminate as mycosis fungoides. One of the early examples of such transformation occurred in a patient under my care in whom for 23 years there was a clinical picture of the disseminate type of parapsoriasis, so diagnosed at various times by leading European and American dermatologists. Within a few days after the patient was exposed to severe cold while duck hunting, the clinical picture changed abruptly, intense pruritus set in, and tumors of mycosis fungoides began to develop. Death occurred a year later.

I believe that the disorder in the case presented today could qualify as being in the premycotic stage of parapsoriasis.

Ichthyosis Associated with Hodgkin's Disease. Presented by DR. JAMES WEBSTER, DR. SAMUEL BLUEFARB, and (by invitation) DR. J. F. SICKLEY.

The patient is a 22-year-old Negro man who was admitted to the hospital on Feb. 22, 1951. He stated that 11 months previously he noticed "a little knot" in the left axilla. This has gradually enlarged to the size of a small grapefruit. The mass at present is slightly painful, and he states that there has never been any drainage from the mass. In the past year he has lost about 23 lb. (10.4 kg.). He also noticed that at about the same time that the mass appeared in the left axilla, his skin was becoming very dry. He states that occasionally his arms "itch slightly."

Upon physical examination the patient presents a large, firm mass in the left axilla. There is no other significant adenopathy. The skin is dry to touch and on the lower extremities there is slight scaling. There is also a moderate follicular keratosis. The liver is palpable 2 fingerbreadths below the costal margin, and the tip of the spleen is palpable on deep inspiration.

The patient has been treated with 15 mg. of triethylene melamine, 5 mg. orally on three successive days. Following this treatment there has been a slight decrease in the size of the mass in the left axilla.

The laboratory findings were as follows: hemoglobin, 31; red blood cells, 1,790,000; white blood cells, 5,400, with 56% neutrophils, 22% neutrophilic band cells, 1% eosinophils, 19% lymphocytes, and 2% mononuclear leucocytes. Serologic reactions were negative. Urinalysis disclosed albumin (3+). Glucose tolerance was normal. Blood culture produced no growth. A chest roentgenogram showed no definite evidence of mediastinal adenopathy. Findings from a bone marrow puncture were as follows: The marrow was moderately hypercellular. Megakaryocytes were slightly increased in number. The ratio of nucleated red blood cells to white blood cells was 1 to 3. Erythropoiesis was normoblastic. Granulopoiesis was intact and slightly toxic.

The report of a lymph-node biopsy was Hodgkin's lymphogranulomatosis.

DISCUSSION

DR. LEON GOLDMAN, Cincinnati: I do not believe that this is ichthyosis. The temptation to use an orally administered nitrogen mustard like triethylene melamine is great in dermatology, but the severe hematopoietic reactions almost contraindicates its use in some instances. Good results have been reported in leukemia and Hodgkin's disease and by Karnofsky in mycosis fungoides. Treatment should not be used unless you have a hematologist in consultation. We are using another type of orally administered nitrogen mustard in mycosis fungoides and in leukemia cutis. So far, in the dosages we have employed, we have had no results. In one patient with mycosis fungoides triethylene melamine was of no benefit. At the suggestion of Haserick we are also trying larger doses of intravenously administered nitrogen mustard together with cortisone.

DR. S. M. BLUEFARB: Ichthyosis associated with Hodgkin's disease has been previously reported (ARCH. DERMAT. & SYPH. **47**:778 [June] 1943, and **50**:85 [Aug.] 1944). This patient stated that as long as he could recall he had a dry skin. However, since the adenopathy appeared, the dryness on his legs had become more marked until, at present, he shows an ichthyotic skin on the lower extremities.

The hematology department of Cook County Hospital has now treated 27 patients with various types of lymphoblastoma with an oral form of nitrogen mustard called triethylene melamine. The total dosage used is 15 mg. administered in 5 mg. tablets for three successive days. The drug must be taken on an empty stomach. The toxic reactions are the same as those from intravenously administered mustards, and the advantage of the oral form is the ease of administration. It is too early to speculate on the results of this form of therapy, but to date the best response has been in Hodgkin's disease, mycosis fungoides, and lymphosarcoma.

Acute Leukemia with Leukemic Ulcers of the Thigh and Ulcers of the Mouth Due to "Aminopterin." Presented by DR. JAMES WEBSTER, DR. SAMUEL BLUEFARB, and (by invitation) DR. J. F. SICKLEY.

The patient is a 24-year-old white man. In the past year his weight has dropped from 135 lb. (61 kg.) to 98 lb. (44.5 kg.). Until one month ago he weighed 118 lb. (53.5 kg.), but at that time "flu" developed and he became very weak. Following this he noticed enlargement of the nodes in the left inguinal region and treated these with hot soaks. He was then taken to a hospital and received 1,000 cc. of whole blood and liver shots. He was then transferred to the Cook County Hospital.

One year ago he suffered with epigastric pain. Roentgenograms were made, and he was told he had "an ulcer high up in the stomach."

On Feb. 24, 1951, a diagnosis of acute myelogenous leukemia was made by the hematology department, and the patient was treated with 2 mg. of "aminopterin" (4-aminopteroyl glutamic acid, a folic acid antagonist) orally, daily. After the first day of therapy the lower lip became edematous, and eight days later superficial ulcerations developed on the buccal surface of the lower lip and along the gum line. The patient has since refused further therapy.

Physical examination upon admission revealed moderate hypertrophy of the gums and a "white lesion on the left lateral aspect of the tongue." There were a few petechiae on the hard palate. In the cervical region there were discrete, small, movable, bilateral nodes. There were also enlarged axillary, inguinal, and epitrochlear nodes. The liver was palpable 1 fingerbreadth below the costal margin, and the spleen was questionably palpable.

In the left inguinal region there is a large ecchymotic patch with two crusted, ulcerated lesions. In the posterior cervical region there is also a large, infiltrated ecchymosis that has not ulcerated. In the mouth there are several superficial erosions along the gum borders and the buccal surface of the lower lip.

Laboratory findings were as follows: + albumin in the urine, normal glucose tolerance, 67% hemoglobin, red blood cells 3,850,000, and white blood cells 21,000, with 3% neutrophils, 4% neutrophilic band cells, 13% blastocytes, 29% lymphocytes, and 49% mononuclear leucocytes. Chest roentgenograms were normal. Serologic reactions were negative. The total serum protein was 7.3 gm. per 100 cc.; uric acid, 6.1 mg., and nonprotein nitrogen, 34 mg. per 100 cc.

The bone marrow is hypercellular. Megakaryocytes are markedly decreased in number. The ratio of nucleated red blood cells to white blood cells is 1 to 6. Erythropoiesis is normoblastic. Granulopoiesis is almost completely replaced by myeloblasts. There is slight increase in basophils, plasma cells, and lymphocytes. The findings are those of acute myelogenous leukemia.

DISCUSSION

DR. LEON GOLDMAN, Cincinnati: I think those large verruca-type lesions are interesting as part of the reaction to the drug. The dermatologist should be aware that children may get an alopecia as a result of the use of "aminopterin." Curiously, this alopecia may improve even though the drug is continued. As far as I am aware, such alopecia reactions are not found in adults. This is additional proof of the greater "lability of reaction" of the hair of children.

DR. S. M. BLUEFARB: This patient has acute myelogenous leukemia, and although it is true that skin lesions are not as common in chronic myelogenous leukemia as in chronic lymphatic leukemia or chronic monocytic leukemia, purpura and hemorrhages do occur in the acute form of myelogenous leukemia due to the marked decrease in megakaryocytes, as seen in the marrow of this patient. Treatment has consisted of the folic acid antagonist, "aminopterin," 2 mg. daily for seven days, a total of 14 mg. On admission, the white blood cell count was 14,400. After seven days of "aminopterin" therapy the white count dropped to 4,000, and toxic symptoms (ulcers of the mouth) of "aminopterin" appeared. The patient was then treated with folinic acid (citrovorum factor) in doses of 40,000,000 units daily. After seven days of this therapy the white blood cell count rose to 54,000. It was thought that by combining the two drugs, "aminopterin" and citrovorum factor, toxic reactions could be avoided. This was done for three days, but the patient refused further therapy. The last blood count showed a drop in all the cellular elements. The probability now is that an aplastic bone marrow is developing.

A Case for Diagnosis: Prurigo Nodularis? Presented by DR. HARRY M. HEDGE.

Prurigo Nodularis. Presented by DR. MALCOLM C. SPENCER, Danville, Ill. (by invitation).

Xanthomatosis with Hypercholesterolemia. Presented by DR. M. H. EBERT and (by invitation) DR. B. YAFFE.

Xanthoma Diabeticorum. Presented by DR. JAMES WEBSTER, DR. SAMUEL BLUEFARB, and (by invitation) DR. STEFAN BIELINSKI, for DR. HERBERT RATTNER.

Case for Diagnosis: Darkening and Pitting of Face and Neck. Presented by DR. THEODORE CORNBLEET.

Lichen Planus with Predominant Involvement of Mucous Membrane. Presented by DR. A. M. BUCHHOLZ and DR. R. B. STOUGHTON (by invitation).

Pemphigus (Foliaceus?) Treated with Corticotropin (ACTH) and Cortisone. Presented by DR. E. A. OLIVER and staff.

Bullous Eruption; Pemphigus Vulgaris(?). Presented by DR. THEODORE CORNBLEET, DR. DAVID COHEN, and (by invitation) DR. J. F. SICKLEY.

Acrokeratosis Verruciformis (Hopf)(?). Presented by DR. CLARK W. FINNERUD and DR. FREDERICK J. SZYMANSKI.

Circumscribed Scleroderma. Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. CALVIN J. DILLAHA.

Papulonecrotic Tuberculid. Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. E. FARNEY-DAVIES.

Lupus Vulgaris. Presented by DR. JAMES WEBSTER, DR. SAMUEL BLUEFARB and (by invitation) DR. STEFAN BIELINSKI, for DR. HERBERT RATTNER.

A Case for Diagnosis: Granuloma Annulare? Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. E. J. VANSCOTT, Buffalo.

Granuloma Annulare. Presented by DR. DAVID OMENS, (by invitation) DR. HAROLD OMENS, and (by invitation) DR. J. F. SICKLEY

Porokeratosis (Mibelli)(?). Presented by DR. I. M. FELSHER (by invitation), DR. A. GOLDBERG and (by invitation) DR. S. MESIROW.

A Case for Diagnosis: Lupus Erythematosus? Presented by DR. EDWARD A. OLIVER and staff and (by invitation) DR. MALCOLM SPENCER.

Discoid Lupus Erythematosus? Presented by Dr. Malcolm C. Spencer, Danville, Ill. (by invitation).

A Case for Diagnosis: Lymphoblastic Nodules? Presented by Dr. James R. Webster and (by invitation) Dr. Oliver Rian.

Lymphogranuloma Venereum with Elephantiasis. Presented by Dr. E. M. Smith.

A Case for Diagnosis: Pityriasis Rubra Pilaris? Presented by Dr. Stephen Rothman, and (by invitation) Dr. Calvin J. Dillaha.

Nevus Unius Lateralis. Presented by Dr. Stephen Rothman and (by invitation) Dr. Harold M. Schneidman.

A Case for Diagnosis: Tertiary Syphilis? Tuberculosis? Presented by Dr. Theodore Cornbleet, Dr. David Cohen, and (by invitation) Dr. Stefan Bielinski.

Localized Myxedema. Presented by Dr. James Webster, Dr. Samuel Bluefarb, and (by invitation) Dr. Stefan Bielinski for Dr. Herbert Rattner.

Koilonychia with Tongue Changes of Iron Deficiency Anemia. Presented by Dr. James Webster, Dr. Samuel Bluefarb, and (by invitation) Dr. J. F. Sickley.

Kaposi's Varicelliform Eruption. Presented by Dr. David Omens, (by invitation) Dr. Harold Omens, and (by invitation) Dr. J. F. Sickley.

Dermatitis Vegetans of the Crural Region (Probably of Mycotic Origin). Presented by Dr. Theodore Cornbleet, Dr. Henry Schorr, and (by invitation) Dr. J. F. Sickley.

DETROIT DERMATOLOGICAL SOCIETY

A. E. Schiller, M.D., *President*

C. J. Courville, M.D., *Secretary*

R. H. Holmes, M.D., *Recorder*

Feb. 14, 1951

Presentation of all cases at this meeting was made by Dr. F. Blumenthal and staff, Department of Dermatology, Wayne County General Hospital, Eloise.

Blastomycosis(?).

R. M., a 50-year-old Negro man, a janitor, complained of sores on the neck, the shoulders, and the left eyebrow, which had been gradually increasing since November, 1949. He recalled a sore on the back of the neck seven years ago which required 2 to 3 years for healing. He appears chronically ill, but no abnormalities are apparent except the skin lesions which are large ulcerative granulomatoses with raised borders.

Laboratory findings indicated a microcytic hypochromic anemia. Biopsy findings were compatible with blastomycosis. Roentgenograms of the chest revealed a peribronchial infiltration not typical of blastomycosis. This resolved later.

The use of iodides resulted in healing of the sores, but toxicity developed. Local administration of 1% "propamidine" (a proprietary compound, 4,4'diamidinodiphenoxy-propane dihydrochloride) did not accelerate healing. During a rest period of 3 months the lesions recurred.

DISCUSSION

Dr. L. W. Shaffer: The scarring, the localization of lesions, and the chronicity favor a diagnosis of lupus vulgaris (tuberculosis luposa). However, I cannot account for the complete recovery and relapse.

Dr. David Kahn, Lansing: A clinical characteristic of lupus vulgaris is its fragility when examined with the rounded end of a probe. Slight pressure will pierce the epidermis.

Dr. H. Pinkus: The lesions of this man are clinically lupus vulgaris. I favor this diagnosis unless blastomyces can be demonstrated in culture or tissue sections.

Ichthyosis: Response to Vitamin-A Therapy.

E. H., a 16-year-old girl, had typical ichthyosis of the trunk and the extremities since infancy. After one month of using liquid petrolatum with salicylic acid topically and 150,000 units of vitamin A ("apexol") daily, marked improvement was noticed. When the use of these medications was discontinued, there was marked relapse.

DISCUSSION

Dr. J. R. Rogin: The results of treatment with vitamin A for ichthyosis have been a great disappointment to me.

Recklinghausen's Disease (Neurofibromatosis); Paresis.

H. W., a 68-year-old Negro man with laboratory-proved and clinically evident paresis, shows extensive neurofibromatosis.

DISCUSSION

DR. L. SHAFFER: This unusual and extensive case of neurofibromatosis is almost a museum piece. I have been surprised to find it stated in the literature that cancer develops in 15% of these cases. Offhand I do not remember ever seeing a case in which cancer has developed.

DR. J. R. ROGIN: I have recently observed a case in which some of the lesions developed into fibrosarcoma.

DR. HARTHER KEIM: I do not recall cancers in these cases.

DR. CHESTER DOTY: I do not recall cancers in these cases.

DR. UDO J. WILE: I have seen small fibromas become malignant.

Purpura Simplex.
Skin Changes Associated with Myxedema.
Hippocratic Nails(?).
Carcinoma of Left Maxillary Sinus.
Epithelioma of Lip.
Psoriasis with Arthritis.
Pellagra(?).
Lymphocytoma Cutis.
Erythema Multiforme(?).
Systemic Blastomycosis.

LOS ANGELES DERMATOLOGICAL SOCIETY

Mollerus Couperus, M.D., *Chairman*

Ben A. Newman, M.D., *Secretary*

Feb. 13, 1951

Granuloma of Undetermined Origin (Cryptococcosis). Presented by DR. J. WALTER WILSON and (by invitation) DR. JOHN W. HILLIARD.

Mrs. L. P., a 61-year-old housewife, accidentally scratched the anterior surface of the right lower leg in April, 1950. At about the time that this initial lesion appeared to heal, she struck the same area against a chair leg and reopened the wound. About three weeks later she again struck the original area and severely bruised it. Following this third episode the lesion began to spread from the initial spot with the result that in a period of four months it had progressed from the lower leg up to the knee, in a horseshoe-shaped lesion with healing in the center and a verrucous elevated border, in the periphery of which were studded a multitude of pinhead pustules and a ring of erythema. New lesions had appeared meanwhile on the medial aspect of the leg, and in December, 1950, similar small pustular lesions occurred on the left leg, being most numerous in the area just distal to the popliteal space. This patient is also under the care of her family physician for hypertension and is receiving a medication for this condition which contains neither bromides nor iodides. The patient takes no other medication except acetylsalicylic acid occasionally.

The blood count and results of urinalysis were normal. Serologic reactions for syphilis were negative. A culture on Sept. 16, 1950, showed scant growth of Micrococcus pyogenes var. albus and M. pyogenes var. aureus, and culture of a biopsy plant on Oct. 17, 1950, showed a gelatinous culture of encapsulated organisms, with no mycelial growth. Three biopsy specimens have been taken at monthly intervals and are presented with the patient.

Before coming under my care the patient was treated with a variety of local medications, including 4,000,000 units of penicillin, without change in the lesion. Further therapy consisted of administration of penicillin; aureomycin; terramycin; wet dressings of silver nitrate and potassium permanganate; local injections with bacitracin in 2% procaine, 500 units per cc. (a total of about 30 cc.) being used by infiltration; strong iodine solution for one month, and superficial x-ray therapy, with no one lesion receiving more than 450 r unfiltered.

As a result of this therapy there has been apparent healing of the lateral border of the lesion of the right leg, which was at the site of the bacitracin injection. New lesions have appeared in spite of therapy, not only on the left leg but even in the area of previous healing on the right leg.

DISCUSSION

DR. L. H. WINER: I found Saccaromyces spores in the intraepidermal pustule of the histologic section.

DR. NELSON PAUL ANDERSON: The histologic section is practically identical with one presented last May in San Diego, in showing the organisms of Cryptococcus.

DR. J. WALTER WILSON: I admit that I am responsible for the presentation of this case as a granuloma of undetermined origin. At the time the protocol was completed, I considered the evidence for cryptococcosis to be incomplete; indeed, the specimen from the third biopsy, the section which I saw for the first time at this meeting, contains the first conclusive proof of this diagnosis. I must compliment Dr. Hilliard very highly for his tenacity in maintaining his opinion until the correct nature of this rare disorder could be established.

Moniliasis (Systemic?); Chronic Hepatomegaly; Pigmentation. Presented by DR. GORDON MACDONALD and (by invitation) DR. THEODORE M. COHEN.

J. F., aged 14, was referred for treatment of a skin disorder in June, 1949. This boy's history began when he was 15 months old, at which time he presented an enlarged liver and spleen and an eruption on the cheeks. He was hospitalized at Children's Hospital for six months and a fatal prognosis was made.

The possibility of syphilis was ruled out, and a biopsy of the liver done at a later date resulted in a diagnosis of chronic fibrous hepatitis. The patient was admitted repeatedly to the Children's Hospital (April, 1938; December, 1941, and February, 1943) for "recurrent epidermophytosis, generalized fungous infection, and chronic hepatitis." A biopsy of a lymph node done in 1938 ruled out Hodgkin's disease, which was suspected at this time.

In 1941 the consulting skin specialist felt that the lesions represented a superficial fungous infection. Liver function tests done at the time of the first admission did not indicate any liver dysfunction. A complete blood count at this time was normal. A culture done by Dr. Chambers in 1944 and again in 1947 was positive for Candida albicans. No x-ray treatment was given at this time.

In 1945, it was reported that the patient had a bone-age delay of three years; and this delay was of two and one-half years in 1947. The basal metabolic rate was —25, the total blood cholesterol was 238 mg. per 100 cc., and the sedimentation rate was rapid. In November, 1948, the patient had several unusual convulsions. After a study, including electroencephalography, it was suggested that the patient had a lowered convulsion threshold, probably on a basis of retarded cerebral development.

The physical examination revealed a fairly well-nourished boy, aged 13, 57¾ in. (146.8 cm.) tall, weighing 73 lb. (33 kg.), with a temperature of 98.4 F. The head was small and gnome-like with a relatively big mouth. There was a moderate blepharitis and conjunctivitis. The ears were normal, and there was a serous discharge from the nose. The mucosa of the mouth was covered with white moist-looking patches. The tongue surface was naked, with a feathered edge except for a few white plaques. There was a dull area in the lower lobe of the right lung posteriorly. The liver was palpable at the costal margin. The skin presented numerous patches of atrophy and alopecia in the scalp which were studded with pustules. The palms and soles were covered with numerous pustules and areas of erythema superimposed upon a depigmented surface. The pustules were also present on the fingers and backs of the hands. Some fingernails and toenails were normal, and others were thick and hyperkeratotic, black, and pyramidal. These hyperkeratotic nails fragmented easily.

Treatment was directed toward the patient's nutritional status and eradication of the pustular infection of the hands and feet. The patient was given a high vitamin diet with supplementary vitamins; and permanganate and Alibour solution (copper sulfate, zinc sulfate, and camphor water) soaks were used intermittently over long periods of time. Iodochlorhydroxyquin (vioform®) cream, ammoniated mercury ointment, nitrofurazone (furacin®) soluble dressing

were used locally. The pustular infection disappeared almost completely for several periods of time from June, 1949, to February, 1950. On the latter date there was an acute flare-up of the pustular infection of the hands and feet.

The patient was hospitalized and treated with continuous wet dressings until the infection subsided. Penicillin and aureomycin were administered. In three weeks all signs of infection were gone, and the patient was operated upon and all the infected nails were removed. The patient went home, and after one week the pustular infection recurred. This time the lesions failed to respond to soaks, ointments, and antibiotics.

Oral use of undecylenic acid was suggested for its effect on the patient's fungus background. Within 3 days the eruption began to clear, and in 10 days all signs of infections were gone. All other treatment was stopped. Six capsules of "sevinon" (an oral undecylenic acid preparation) was administered daily, and the amount was gradually increased to fifteen capsules daily over a three-week period.

From April, 1950, when the "sevinon" treatment was begun until the present time, we attempted to withdraw the drug on four different occasions, and each time pustules and inflammatory areas appeared on the hands and feet within 48 hours. Upon resumption of the use of the drug, the pustules cleared. We have reduced the dosage of undecylenic acid to six capsules daily. This seems to be the maintenance dose. In December, 1950, the patient was hospitalized for an attack of tracheobronchitis.

It has been noted that for the past five months the patient has been gradually showing an increase of pigment in all areas of the skin, especially about the genitalia and axillae. Dark lentigo-like lesions have appeared in large numbers on the trunk. The patient now looks like an Indian. This increase in pigmentation appears to be due to the undecylenic acid. Only crude liver extract and injectible vitamins (vi-syneral®) have been used, in addition to the undecylenic acid, in the past six months.

The results of laboratory examination are as follows: The Wassermann reaction was negative; the urine has shown occasional traces of albumin; the blood count is normal; the blood iodine, results of liver function and glucose tolerance test, and roentgenograms of the chest were normal, and a culture from the mouth lesions showed Candida albicans.

A microscopic slide of an elevated dark papule reveals the epidermis to be normal with a regular intact basal layer, the cells containing large amounts of pigment. The cutis is filled with many nests of nevus cells, and pigment is scattered throughout these nests of cells and stroma.

This case is presented because of the long history of chronic infection, the response to undecylenic acid, and the recent marked pigmentation thought to be due to this drug.

Suggestions as to further therapy and management would be greatly appreciated.

DISCUSSION

DR. KENNETH L. STOUT: About seven years ago I first saw this patient after a physician in San Bernardino had removed all the fingernails. Shortly before I saw him, he had had a complete medical examination and study in the Children's Hospital and, under Dr. Clyde Wood's care, had received a number of blood transfusions and intensive parenteral riboflavin therapy. There was a history of tinea capitis (Microsporum audouini) which had been epilated by x-rays. At that time the scalp showed several areas of partial alopecia but no evidence of inflammation, although there were numerous comedones, many of the double type, in the scalp.

He presented the clinical picture of perlèche and a thrush-like condition in the mouth. On the palms and soles were vesicopustules. There was no vitiligo at that time. The child had been receiving thyroid, 0.5 grain, for six months. At that time, it was my recommendation that this child be studied thoroughly from a metabolic standpoint. I remember obtaining a pure culture of Candida from the palm and sole lesions. At that time, the glucose tolerance curve was almost flat. The fasting blood sugar was 110 mg. per 100 cc.; after one-half hour it was 120 mg., and at the end of three hours, 90 mg.

Over a period of three to four months this child did fairly well from a general standpoint, and the lesions on the hands and mouth cleared up. During this period he received heavy doses of vitamin B complex fortified with riboflavin and nicotinamide. At that time the child's pediatrician

reported that in his opinion the child was normal in physical and mental growth. I encouraged further studies, and apparently these were not done by the chief of the diabetic clinic at the Cedars of Lebanon Hospital.

DR. J. WALTER WILSON: I wish to recall a case presented from the University of Chicago, a complete exhibit of systemic moniliasis. I wish to remind you that Candida albicans must have to find a nice place to invade. To my mind, there must be a generally disturbed metabolism in this boy that paves the way for moniliasis.

DR. NELSON PAUL ANDERSON: Years ago Dr. Ayres and I had a patient who had similar changes in the mouth, on the tongue, with monilial involvement of all fingernails. He eventually died of pneumonia. I think that Dr. Cohen's patient has adrenal cortical hypofunction (Addison's disease) due to Candida albicans involving the adrenals, rather than tuberculosis. I would warn anyone against administering either aureomycin, terramycin, or chloromycetin, and possibly penicillin, in the presence of proved Candida infection. At the last Academy meeting, Dr. Zola Cooper presented the case of a child who had received several courses of antibiotic therapy. He died, and when an autopsy was done there were organisms of Candida albicans in the kidney, the liver, and other internal organs. I think this child also has Candida albicans in the liver and spleen, producing hepatosplenomegaly. The dark, deep-bronzed pigmentation, in addition to the vitiliginous areas of the hands and feet, the pigmentation of the numerous moles, and the darkening of the areola, are rather characteristic of adrenal cortical hypofunction. I think Kepler's water test should be done to determine the possibility of adrenal cortical hypofunction. Once the presence of the disease is determined, the patient should receive adequate therapy for that condition, as this is the only way to keep him alive until something can be done to counteract the systemic moniliasis. Undecylenic acid has been used, and no one has reported such a pigmentation from it.

DR. GAGE HELMS: I feel that this patient has moniliasis and most probably some other underlying pathologic condition. I would suggest a biopsy of an inflammatory area.

DR. THEODORE COHEN (by invitation): I wish to thank Dr. Stout for giving us a summary of his history on this same patient. It will help us correlate the entire picture in this case. Dr Cover, the internist now taking care of this boy, recently sent me a summary of his findings, and in that summary stated that it was his belief that the Candida albicans infection was superimposed upon a metabolic disorder. This is in agreement with what Dr. Wilson has just told us. This boy's condition did become aggravated when he was treated with aureomycin while hospitalized. We will follow the suggestions made and will study this boy completely to determine whether his laboratory work will confirm the diagnosis of adrenal cortical hypofunction.

Trichophytic Granuloma (Tinea Profunda) Due to Trichophyton Rubrum. Presented by DR. J. WALTER WILSON.

While square dancing one year ago, Mrs. M. F., a 54-year-old white woman, injured her left leg just above the ankle on the medial surface, with a resulting large bruised area. This swelling and discoloration subsided, but eczema developed near the periphery and has persisted with considerable fluctuation. Pruritus has not been marked; tenderness was noted at times.

In the interim, the area was treated with x-rays on four occasions by a roentgenologist, with temporary benefit only, and a variety of salves were applied. Extensive investigations have revealed no metabolic disorder, and a physician competent in the field of peripheral vascular diseases was reluctant to accept such a diagnosis.

Two weeks ago examination revealed a single oval plaque of dermatitis about 5 by 8 cm. in diameter, dusky red, with considerable scaling. The border was not sharply delineated. Several deep-seated, slightly tender nodules were palpable. Clinical diagnosis was doubtful, but tuberculosis induratum, infectious granuloma, and static dermatitis were considered.

A specimen was removed for biopsy from one of the nodular areas after thorough cleansing of the surface. Several scrapings were taken from the under surface of this specimen and inoculated onto Sabouraud's glucose agar and aerobic and anerobic media. All three cultures on Sabouraud's agar revealed a pure culture identifiable within 10 days as Trichophyton rubrum. Examination of the section stained by hematoxylin and eosin revealed a granulomatous process

extending deeply into the cutis. A careful search failed to disclose fungous elements. When sections were stained with the Hotchkiss-McManus method, however, an oval lobule was seen to take the stain intensely; examination of this area showed it to consist entirely of rounded spores, some in chains, about 2 μ in diameter.

With the above facts in mind, scrapings were taken from several of the more superficial areas at the edge of the plaque. Some of these showed hyphae and arthrospores characteristic of Trichophyton infections. Cultures were inoculated, one of which has begun to show a growth which is as yet unidentifiable.

DISCUSSION

DR. M. E. OBERMAYER: My original clinical diagnosis of this patient's disease was stasic dermatitis with localized capillary thrombophlebitis. I assured Dr. Wilson that an infectious granuloma was impossible. Somewhat stubbornly, I thought, he insisted on biopsy and inoculated cultures from the deep surface of the specimen. As a consequence, we now have a beautiful demonstration of the necessity for continually checking our clinical impressions by laboratory procedures, even when they seem most conclusive.

DR. W. H. GOECKERMAN: I should like to commend Dr. Wilson for presenting this case with a clinical diagnosis. I doubt if I would have suspected this lesion clinically as being mycotic. Even a biopsy with an ordinary hematosic eosin stain evidently would not have indicated the diagnosis.

DR. L. H. WINER: The microscopic section contained intraepidermal abscesses, typical features seen in bromoderma or blastomycosis. With the Hotchkiss-McManus stain, these intraepidermal abscesses were seen to contain masses of spores. These were smaller than those of blastomyces, and there was no budding.

DR. J. WALTER WILSON: We are taught that trichophytons do not penetrate deeper than the basal layer of the skin unless fortified by bacterial association or allergic phenomena. In the present instance, cultures revealed T. rubrum in the deepest portions of the biopsy specimen. Examination of the specimen stained with hematoxylin and eosin failed to reveal fungous elements, but the Hotchkiss-McManus stain brought to view localized spherical accumulations, perhaps 30 μ in diameter, of rounded fungous spores without hyphae. These areas are much too deep to be explained as follicular invasions in an area supplied only with lanugo hairs. Dr. Obermayer and I have observed three cases previously in which T. rubrum caused a granulomatous process in many follicles in areas on the legs, from which extracted hairs revealed an ectothrix mantle of large spores and positive cultures. That penetration can occur deeper than the follicles extend is an entirely new concept worthy of further study.

Lichenoid Tuberculid and Tuberculosis Papulonecrotica (Folliclis) (?). Presented by DR. L. H. WINER and (by invitation) DR. M. C. ZIMMERMAN.

Scleroderma in a Six-Year-Old Girl. Presented by DR. GAGE HELMS and DR. R. W. HELMS.

Koilonychia. Presented by DR. M. D. KNOLL.

Chronic Discoid Lupus Erythematosus and Pregnancy. Presented by DR. M. J. WOLFF.

Pigmented Nevus. Presented by DR. JOHN D. ROGERS.

Alopecia Cicatrisata. Presented by DR. M. E. OBERMAYER and (by invitation) DR. ERNEST FOX.

Epidermolysis Bullosa with Pigmentary Anomaly. Presented by DR. K. L. STOUT.

Pseudoxanthoma Elasticum with Angioid Streaks in Retina. Presented by DR. L. H. WINER.

News and Comment

ANNOUNCEMENT

Dermatology will be the subject of a continuation course for general physicians to be presented by the University of Minnesota, Feb. 28 to March 1, 1952. Dr. Arthur C. Curtis, Professor and Chairman of the Department of Dermatology, University of Michigan, will be the visiting faculty member for the course. The course will be presented under the direction of Dr. Henry E. Michelson, Chairman of the Divison of Dermatology at the University of Minnesota.

Book Reviews

Lehrbuch der Haut- und Geschlechtskrankheiten. By W. Lutz, Professor and Director of the Department of Dermatology of the University of Basel, Switzerland. Price, 64 francs. Pp. xr, 658, with 375 illustrations. S. Karger Verlag, Basel and New York, 1951.

This German language textbook by the well-known Swiss dermatologist, W. Lutz, who also is editor of the international journal *Dermatologica*, combines tenets of the German and French schools of dermatology with ample references to American views and a rich background of personal experience. The first pages offer concise and well-chosen information on morphology, physiology, and chemistry of the skin. The next chapters, on clinical diagnosis, etiology, systematics, and pathogenesis, truly constitute a propaedeutic of dermatology which will be read with great advantage by the beginner, and make a thought-provoking refresher course in the basic principles of the specialty for anybody. The chapters on therapy contain an excellent survey of current European thinking and give many formulae. In the larger special part of the text, the author has striven successfully to delineate clearly the clinical manifestations of skin diseases according to von Hebra's teachings and to arrange the dermatoses in conformity with etiologic and pathogenetic principles. The accomplishment of the first goal is assisted by approximately 500 carefully chosen and excellently reproduced clinical photographs and a number of reproductions of micro-organisms and parasites. In the execution of his second purpose, the arrangement of dermatoses in a logical etiologic system, Lutz makes extensive use of Brocq's concept of *réactions cutanées*. This concept stresses the predisposition of one person's skin to react to various external causes with similar manifestations, and of different persons to respond to an identical stimulus with dissimilar eruptions.

Lutz's announced purpose is to survey the field of dermatology as completely as possible, but to treat the commoner diseases more thoroughly. Without going into details, two points may be mentioned which indicate the author's thinking and which may be less familiar to American readers. Darier's kerosis, a state of diminished suppleness of the skin due to increased coherence and reduced shedding of the horny lamellae, is accepted by Lutz as an important soil for the development of seborrheic manifestations, including acne vulgaris and rosacea. Under the name dermoepidermitis, the author combines as a clinical entity manifestations which have been described under many different terms, including nummular eczema, microbic eczema, bacterids, levurids, infectious eczematoid dermatitis, etc. Lutz differentiates an erosive moist type due exclusively to external factors, such as maceration, friction, and bacterial infection, and an erythematous squamous type due to impaired circulation and nutrition of the skin and of the epidermis in particular.

The book, like all European texts, contains a chapter on gonorrhea in addition to the material usually covered in American treatises. Short descriptions of the typical histologic features of many dermatoses enhance the value of the book. Print and paper are excellent. The picture material, while not as profuse as in some recent American texts, is ample and especially well chosen. The reader's convenience would be served if the clinical photographs were identified

by diagnosis rather than just by number. There is a good index. Bibliographic references are omitted in conformity with European usage. The language is clear and easily readable. The book is highly recommended to any American physician, and particularly dermatologist, who wants to acquaint himself with modern Continental knowledge and thinking in the field of dermatology and venereal diseases.

Regional Dermatologic Diagnosis: A Practical System of Dermatology for the Non-Specialist. By Ervin Epstein, M.D. Price, $6. Pp. 328, with 148 illustrations. Lea & Febiger, Philadelphia, 1950.

This book will find favor with the busy general practitioner who, in observing, for example, an eruption on the ear, need only turn to the page or chart listing the possibilities as to regional diagnosis. The advisability of breaking dermatology down into specific regions as a means of diagnosing and/or treating disease entities may be debatable. The book is well organized, however, and the illustrations seem to depict well the intended entities.

Although Dr. Epstein has intended this book for nondermatologists and students, the latter may be misled by the apparent ease with which a diagnosis may be made, merely by the location of the process. It seems more advisable in evaluating a dermatologic problem to view the patient as a whole and not by isolated segments of his body.

Appendix A, which mentions briefly the commonest dermatoses, and Appendix B, listing some of the commoner therapeutic measures, are definitely of value to the practicing physician. Appendix C, listing some of the cutaneous manifestations of systemic disease, is a brief but important portion of the text.

Dermatologists and other physicians will find this book of value in the differential diagnosis of regional dermatologic problems.

CORRECTION

In the article by Drs. Franks, Rosenbaum, and Mandel on "Trichophyton Sulfureum Causing Erythema Nodosum and Multiple Kerion Formation," in the January issue, page 96, the last sentence should read "We had the opportunity to observe with Dr. M. Jessner a patient with kerion formation due to Microsporum lanosum associated with a papulofollicular eruption on the chest and erythema-nodosum-like lesions on the upper extremities."

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*Harrison, T. R.: *Principles* of *Internal Medicine*, Philadelphia, The Blakiston Company, 1950, p. 981

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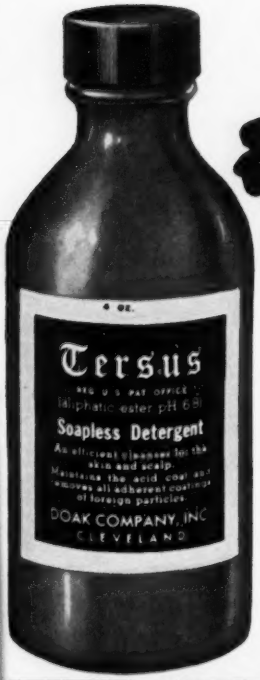

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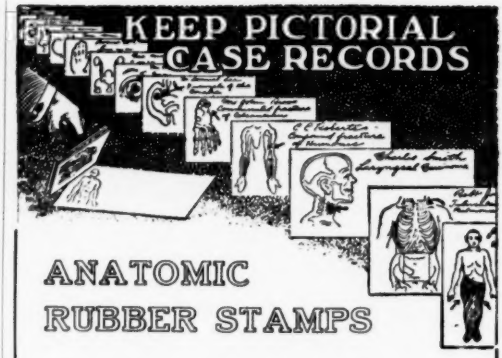

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2. Combes, F. C.: Coal Tar in Dermatology. Arch. Dermat. and Syph. **56**:583-588 (Nov.) 1947.
3. Ellis, C. C.: Wooldridge, W. E., and Weiss, R. S.: J. Invest. Dermat. **10**:6 (June) 1948.

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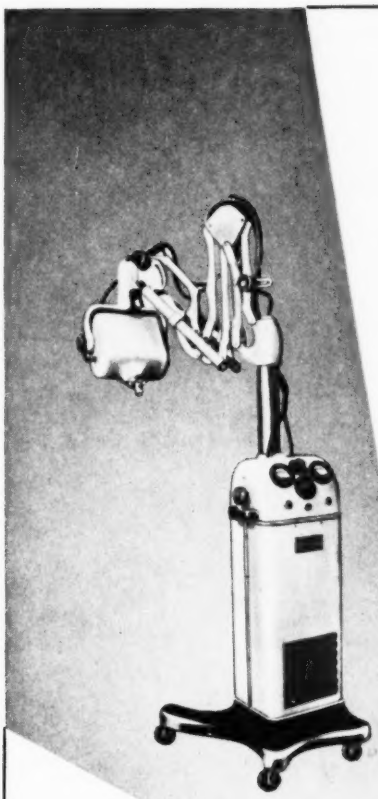

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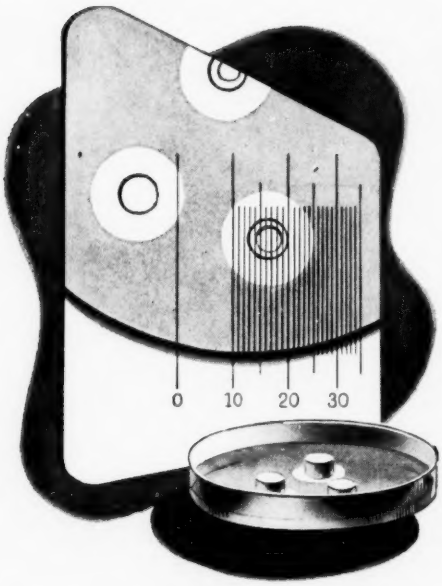

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